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(57) Abstract

Peptides which are peptide derivatives of the αD region of a protein kinase can modulate the activity of protein kinases. The activity of a protein kinase in a subject can be modulated by administering one or more of these peptides.

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SHORT PEPTIDES WHICH SELECTIVELY MODULATE THE ACTIVITY OF PROTEIN KINASES

BACKGROUND OF THE INVENTION

There are a group of proteins that constitute the eukaryotic protein kinase superfamily. Enzymes of this class specifically phosphorylate serine, threonine or tyrosine residues of intracellular proteins. These enzymes are important in mediating signal transduction in multicellular organisms. Many of the protein kinases are part of transmembrane receptors. Others occur as intracellular proteins which take part in signal transduction within the cell, including signal transduction to the nucleus and activation of other proteins. Other protein kinases, such as G protein-coupled receptor kinases, are bound to cell membranes and participate in transmembrane signalling.

As such, phosphorylation of serine, threonine or tyrosine by protein kinases is an important mechanism for regulating intracellular events in response to environmental changes. A wide variety of cellular events are regulated by protein kinases. A few examples include cellular proliferation, cellular differentiation, the ability of cells to enter and/or complete mitosis, cellular transformation by RNA viruses, oncogenesis, control of fat metabolism, immune responses, inflammatory responses and the control of carbohydrate metabolism.

Enhanced protein kinase activity can lead to persistent stimulation by secreted growth factors and other growth inducing factors which, in turn, can lead to proliferative diseases such as cancer, to nonmalignant proliferative diseases such as arteriosclerosis, psoriasis and to inflammatory response such as septic shock. Decreased function can also lead to disease. For example, a decrease in the activity of insulin receptor kinase is a cause of various types of diabetes. Severe reduction of the B cell progenitor kinase leads to human X-linked agammaglobulinemia.

Thus, agents which can modulate (increase or decrease) the activity of protein kinases have great potential for the treatment of a wide variety of diseases and conditions such as cancer, obesity, autoimmune disorders, inflammation and diabetes. Such agents also have utility in deciphering the mode of action of protein kinases and how these proteins regulate cellular functions and activities.

SUMMARY OF THE INVENTION

It has now been found that short peptides which are derivatives of the αD region of a protein kinase can significantly affect the activities of cells expressing the protein kinase when incubated with the cells (the "αD region" is defined hereinbelow). For example, the peptide derivatives of the αD region of Jak3 inhibit the proliferation of human endothelial cells and the human prostate cancer cell line PC3 *in vitro* at concentrations as low as 0.3 μM (Example 2). Based on the aforementioned discoveries, novel peptides are disclosed herein which are peptide derivatives of the αD region of protein kinases. Also disclosed are methods of identifying a peptide derivative of an αD region of a protein kinase that modulates the activity of the protein kinase. Methods of modulating the activity of a protein kinase in a subject are also disclosed.

One embodiment of the present invention is a novel peptide which is a peptide derivative of the αD region of a protein kinase. The peptide comprises between about five and about thirty amino acid residues or amino acid residue analogs of the αD region. The peptide modulates the activity of the protein kinase. The N-terminus and/or C-terminus of the peptide can be substituted or unsubstituted. The peptide can be linear or cyclic.

Another embodiment of the present invention is a method of modulating the activity of a protein kinase in a subject. The method comprises administering a therapeutically effective amount of a peptide that is a derivative of the αD region of the protein kinase, as described above.

Yet another embodiment of the present invention is a method of identifying a peptide which modulates the activity of a protein kinase. The method comprises providing a "test peptide" which has from about five to about thirty amino acids or amino acid analogs and which is a peptide derivative of the αD region of the protein kinase. The test peptide is incubated with cells having a cellular activity or function under the control of the protein kinase under conditions suitable for assessing the activity of the protein kinase. The activity of the protein kinase is assessed and compared with the activity of the protein kinase in cells of the same cell type grown under the same conditions in the absence of the test peptide. A greater or lesser

activity compared with cells grown in the absence of the test peptide indicates that the test peptide modulates the activity of the protein kinase.

The peptides of the present invention can be used in the treatment of a wide variety of diseases caused by overactivity or underactivity of a protein kinase. Examples include, but are not limited to, cancer, diseases caused by proliferation of smooth muscle (e.g. restenosis and atherosclerosis), skin disorders, diabetes, obesity, diseases of the central nervous system, inflammatory disorders, autoimmune diseases and other immune disorders, osteoporosis and cardiovascular diseases. The peptides of the present invention also have *in vitro* utilities, for example, in the generation of antibodies that specifically bind the protein kinase from which the peptide was derived. These antibodies can be used to identify cells expressing the protein kinase and to study the intracellular distribution of the protein kinase. In addition, the peptides of the present invention can be used to identity and quantitate ligands that bind the αD region of the protein kinase from which the peptide was derived.

BRIEF DESCRIPTION OF THE FIGURES

Figures 1A-1I are a table illustrating the amino acid sequences of the αD region of the following protein kinases:

c-Raf (SEQ ID NO. 1); Araf (SEQ ID NO. 2); Braf (SEQ ID NO. 3); cyclic AMP dependent protein kinases a, b and g (cAPK) (SEQ ID NO. 4 to 5); protein kinase C alpha through theta (PKC) (SEQ ID NO. 6 to 12); Akt 1 and 2 (also called Rac α and β) (SEQ ID NO. 13); glycogen synthase kinase α and β (GSK3) (SEQ ID NO. 14 to 15); casein kinases type II α and α' (CK) (SEQ ID NO. 16 to 17); G-receptor coupled protein kinases β-2 adrenergic receptor kinases 1 and 2 (bARK1, 2) (SEQ ID NO. 18); G-protein coupled receptor kinases GRK1 and GRK4 through GRK6 (SEQ ID NO. 19 to 22); calmodulin dependent kinases types I and II a, b, c and d (CaMK) (SEQ ID NO. 23 to 24); members of the Polo-associated family: Plk, Plx1, polo, SNK, CDC5, Sak, Prk, Fnk, Plo1 (SEQ ID NO. 25 to 32); MARK1 and MARK2 and p78 (SEQ ID NO. 33 to 34); cyclin dependent kinases 2, 4 and 6 (SEQ ID NO. 35 to 37); Src, Yes, Fyn, Fgr, Lyn, Hck, Lck (SEQ ID NO. 38 to 44); Csk

and Matk (SEQ ID NO. 45 to 46); focal adhesion kinase (FAK) (SEQ ID NO. 47); c-Abl (SEQ ID NO. 48); endothelial growth factor receptors Tie, Tek, FGF receptor (Flg, Bek, FGFR3, FGFR4), PDGF receptor α and β, Flt 1 and 4 and Flk1 (SEQ ID NO. 49 to 59); HGF receptors c-Met, c-Sea and Ron (SEQ ID NO. 60 to 62); EGF receptor (EGFR, ErbB2, ErbB3, ErbB4) (SEQ ID NO. 63 to 66); Ret (SEQ ID NO. 67); NGF receptors (Trk) (SEQ ID NO. 68 to 70); Syk and Zap70 (SEQ ID NO. 71 to 72); Jak kinases 1 through 3 and Tyk2 (SEQ ID NO. 73 to 76); Iak1 (SEQ ID NO. 77); Chk1 (SEQ ID NO. 78); NFkB inhibitor kinases, known also as I-kappa B kinases IKK1 and IKK2 (SEQ ID NO. 79 to 80); death associated protein kinase (DAPK) (SEQ ID NO. 81); insulin receptor kinase (IRK) (SEQ ID NO. 82); TGFβ receptor type II (SEQ ID NO. 83); Activin receptor type II A and B (ACTR) (SEQ ID NO. 84 to 85); Activin receptor-like kinases 1 through 6 (ALK1, 2, 3, 4, 5, 6) (SEQ ID NO. 86 to 90); discoidin domain receptor 1 (DDR) and Tyro10 (SEQ ID NO. 91 to 92); ILK (SEQ ID NO. 93); Jun kinase (JNK) (SEQ ID NO. 94).

Figures 2A-2F are a group of sequences illustrating the consensus amino acid sequences of the αD region found among the family of protein kinases. Also shown are examples of conservative substitutions in these amino acid sequences. An "*" indicates an aliphatic, substituted aliphatic, benzylic, substituted benzylic, aromatic or substituted aromatic ester of glutamic acid or aspartic acid.

Figures 3A-3D are a Table illustrating the sequences of the following peptides:

Akt1/Raca K014D001; ALK1 K048D101; Braf K003D001 K003D101; c-Abl K061D101; c-Met K073D101; c-Raf K001D101 K001D001; c-Sea K074D101; c-Src K051D101 K051D001; CDK2 K049D101 K049D001; CDK4 K050D001 K050D101; CDK6 K089D101; Chk1 K088D102 K088D101; CK IIα K022D001 K022D101; Csk K058D101 K058D001; Fak K060D101; FGFR-3 K071D101 K071D001 K071D102 K071D901; Flk1 K068D102 K068D101 K068D001 K068D901; GSK3ß K018D003 K018D002 K018D101 K018D001; Hck K056D101; Iak1 K087D101; IKK-1 K090D101; IKK2 K091D101; ILK K107D101 K107D901; IRK K094D001 K094D101 K094D102 K094D103 K094D104; Jak1 K084D101 K084D102; Jak2 K085D102 K085D105; Jak3

K086D101 K086D102 K086D103; Lck K057D001 K057D101; Lyn K055D101; MARK1 K045D101; PDGFR-b K064D001 K064D101; PKCß K008D101 K008D001; Plk K035D001 K035D101 K035D102; Ret K080D101 K080D001; Ron K075D101; SNK K038D101; Syk K082D101; TGFβRII K093D101; TrkB K102D101 K102D106 K102D107 K102D108 K102D109; Zap70 K083D101 (SEQ ID NO: 95 to 170, respectively).

Peptides are either N-acetylated, N-stearylated or N-myristylated and C-amidated. "E!" indicates a benzyl ester of glutamic acid and "D!" indicates a benzyl ester of aspartic acid. Figure 3 also indicates from which protein kinase each peptide is derived.

Figure 4 is a graphical representation of the percent change in daily food consumption for CB6F1 mice. Members of the experimental group were administered a Jak2-derived peptide and the members of the control group were administered vehicle alone.

Figure 5 is a graphical representation of the percent change in daily body weight for CB6F1 mice. Members of the experimental group were administered a Jak2-derived peptide and members of the control group were administered vehicle alone.

Figure 6 is a graphical representation of the amount of IL-4 or IFNγ that is secreted by CD4+ T cells that have been incubated with different concentrations of a Jak3 peptide.

DETAILED DESCRIPTION OF THE INVENTION

A protein kinase (hereinafter "PK") is an intracellular or membrane bound protein which uses the gamma phosphate of ATP or GTP to generate phosphate monoesters on the hydroxyl group of a serine or threonine residue, or on the phenolic group of a tyrosine residue. PKs have homologous "kinase domains" or "catalytic domains" which carry out this phosphorylation. Based on a comparison of a large number of protein kinases, it is now known that the kinase domain of protein kinases can be divided into twelve subdomains. These are regions that are generally uninterrupted by large amino acid insertions and which contain characteristic

patterns of conserved residues (Hanks and Hunter, "The Eukaryotic Protein Kinase Superfamily", in Hardie and Hanks ed., *The Protein Kinase Facts Book, Volume I*, Academic Press, Chapter 2, 1995). These subdomains are referred to as Subdomain I through Subdomain XII.

The "αD region" referred to herein is found within the kinase domain of PKs in Subdomain V and the beginning of Subdomain VI. Because of the high degree of homology found in the subdomains of different protein kinases, the amino acid sequences of the domains of different PKs can be aligned. Thus, the αD region of a PK can be defined by reference to the amino acid sequence of a prototypical protein kinase, for example PKA-Cα, and can be said to correspond to a contiguous sequence of about twenty amino acid residues found between about amino acid 120 and 139 of PKA-Cα.

A second definition of the αD region of a PK, which is complementary to the definition provided in the preceding paragraph, can be made by reference to the three dimensional structure of the kinase domain of PKs. The kinase domain of PKs has been found to contain at least nine alpha helices, referred to as helix A through helix I and nine beta sheets, referred to as b1 through b9 (Tabor *et al., Phil. Trans. R. Soc. Lond. B340:*315 (1993), Mohammadi *et al., Cell 86:*577 (1996) and Hubbard *et al., Nature 372:*746 (1994)). The αD region is a contiguous sequence of about fifteen to forty amino acids beginning at the end of the b5 beta sheet and extending through the D helix and the following loop to the beginning of helix E.

Optionally, the C-terminus or the N-terminus of the peptides of the present invention, or both, can be substituted with a carboxylic acid protecting group or an amine protecting group, respectively. Suitable protecting groups are described in Green and Wuts, *"Protecting Groups in Organic Synthesis"*, John Wiley and Sons, Chapters 5 and 7, 1991, the teachings of which are incorporated herein by reference. Preferred protecting groups are those that facilitate transport of the peptide into a cell, for example, by reducing the hydrophilicity and increasing the lipophilicity of the peptide. Examples of N-terminal protecting groups include acyl groups (-CO-R_1) and alkoxy carbonyl or aryloxy carbonyl groups (-CO-O-R_1), wherein R_1 is an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or a substituted

aromatic group. Specific examples of acyl groups include acetyl, (ethyl)-CO-, *n*-propyl-CO-, *iso*-propyl-CO-, *n*-butyl-CO-, *sec*-butyl-CO-, *t*-butyl-CO-, lauroyl, palmitoyl, myristoyl, stearyl, phenyl-CO-, substituted phenyl-CO-, benzyl-CO- and (substituted benzyl)-CO-. Examples of alkoxy carbonyl and aryloxy carbonyl groups include CH_3-O-CO-, (ethyl)-O-CO-, *n*-propyl-O-CO-, *iso*-propyl-O-CO-, *n*-butyl-O-CO-, *sec*-butyl-O-CO-, *t*-butyl-O-CO-, phenyl-O-CO-, substituted phenyl-O-CO- and benzyl-O-CO-, (substituted benzyl)-O-CO-. In order to facilitate the N-acylation, a glycine can be added to the N-terminus of the sequence. The carboxyl group at the C-terminus can be protected, for example, by an amide (i.e., the hydroxyl group at the C-terminus is replaced with $-NH_2$, $-NHR_2$ and $-NR_2R_3$) or ester (i.e. the hydroxyl group at the C-terminus is replaced with $-OR_2$). R_2 and R_3 are independently an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aryl or a substituted aryl group. In addition, taken together with the nitrogen atom, R_2 and R_3 can form a C4 to C8 heterocyclic ring with from about 0-2 additional heteroatoms such as nitrogen, oxygen or sulfur. Examples of suitable heterocyclic rings include piperidinyl, pyrrolidinyl, morpholino, thiomorpholino or piperazinyl. Examples of C-terminal protecting groups include $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, -NH(ethyl), -N(ethyl)$_2$, -N(methyl)(ethyl), -NH(benzyl), -N(C1-C4 alkyl)(benzyl), -NH(phenyl), -N(C1-C4 alkyl)(phenyl), $-OCH_3$, -O-(ethyl), -O-(*n*-propyl), -O-(*n*-butyl), -O-(*iso*-propyl), -O-(*sec*-butyl), -O-(*t*-butyl), -O-benzyl and -O-phenyl.

A "peptide derivative of the αD region" includes a peptide having the amino acid sequence of the αD region. A "peptide derivative of the αD region" also includes a subsequence of the αD region of the PK. A subsequence of a protein region is a contiguous sequence of from about five to about thirty amino acids or amino acid residues found within a larger sequence. Thus, a subsequence of the αD region is a contiguous sequence of from about five to about thirty amino acids or amino acid residues found within the αD region. A subsequence of the αD region can also be referred to as a "fragment" of the αD region.

A "peptide derivative" also includes a peptide having a "modified sequence" in which one or more amino acids in the original sequence or subsequence have been substituted with a naturally occurring amino acid or amino acid analog (also referred

to as a "modified amino acid"). In one aspect of the present invention, the peptide derivative has a sequence corresponding to a subsequence of the αD region of a PK, with the proviso that any one amino acid residue in the peptide derivative can differ from the corresponding amino acid residue in the subsequence. For example, if the subsequence is $[AA_1]$-$[AA_2]$-$AA_3]$-$[AA_4]$-$[AA_5]$, then the peptide derivative can be $[AA_1']$-$[AA_2]$-$[AA_3]$-$[AA_4]$-$[AA_5]$, $[AA_1]$-$[AA_2']$-$[AA_3]$-$[AA_4]$-$[AA_5]$, $[AA_1]$-$[AA_2]$-$[AA_3']$-$[AA_4]$-$[AA_5]$, $[AA_1]$-$[AA_2]$-$[AA_3]$-$[AA_4']$-$[AA_5]$ and $[AA_1]$-$[AA_2]$-$AA_3]$-$[AA_4]$-$[AA_5']$, wherein [AA'] is a naturally occurring or modified amino acid different from [AA]. In another aspect of the present invention, the peptide derivative has a sequence corresponding to a subsequence of the αD region of a PK, with the proviso that any two amino acid residues in the peptide derivative can differ from the corresponding amino acid residue in the subsequence.

An "amino acid residue" is a moiety found within a peptide and is represented by -NH-CHR-CO-, wherein R is the side chain of a naturally occurring amino acid. When referring to a moiety found within a peptide, the terms "amino acid residue" and "amino acid" are used interchangeably in this application. An "amino acid residue analog" includes D or L residues having the following formula: -NH-CHR-CO-, wherein R is an aliphatic group, a substituted aliphatic group, a benzyl group, a substituted benzyl group, an aromatic group or a substituted aromatic group and wherein R does not correspond to the side chain of a naturally-occurring amino acid. When referring to a moiety found within a peptide, the terms "amino acid residue analog" and "amino acid analog" are used interchangeably in this application.

As used herein, aliphatic groups include straight chained, branched or cyclic C1-C8 hydrocarbons that are completely saturated, which contain one or two heteroatoms such as nitrogen, oxygen or sulfur and/or which contain one or more units of unsaturation. Aromatic groups include carbocyclic aromatic groups such as phenyl and naphthyl and heterocyclic aromatic groups such as imidazolyl, indolyl, thienyl, furanyl, pyridyl, pyranyl, pyranyl, oxazolyl, benzothienyl, benzofuranyl, quinolinyl, isoquinolinyl and acridintyl.

Suitable substituents on an aliphatic, aromatic or benzyl group include -OH, halogen

(-Br, -Cl, -I and -F), -O (aliphatic, substituted aliphatic, benzyl, substituted benzyl, aryl or substituted aryl group), -CN, -NO_2, -COOH, -NH_2, -NH(aliphatic group, substituted aliphatic, benzyl, substituted benzyl, aryl or substituted aryl group), -N(aliphatic group, substituted aliphatic, benzyl, substituted benzyl, aryl or substituted aryl group)$_2$, -COO(aliphatic group, substituted aliphatic, benzyl, substituted benzyl, aryl or substituted aryl group), -$CONH_2$, -CONH(aliphatic, substituted aliphatic group, benzyl, substituted benzyl, aryl or substituted aryl group), -SH, -S(aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic group) and -NH-C(=NH)-NH_2. A substituted benzylic or aromatic group can also have an aliphatic or substituted aliphatic group as a substituent. A substituted aliphatic group can also have a benzyl, substituted benzyl, aryl or substituted aryl group as a substituent. A substituted aliphatic, substituted aromatic or substituted benzyl group can have one or more substituents.

Suitable substitutions for amino acid residues in the sequence of an αD region or a subsequence of an αD region include conservative substitutions which result in peptide derivatives which modulate the activity of a PK. A "conservative substitution" is a substitution in which the substituting amino acid (naturally occurring or modified) has about the same size and electronic properties as the amino acid being substituted. Thus, the substituting amino acid would have the same or a similar functional group in the side chain as the original amino acid.

A "conservative substitution" also refers to utilizing a substituting amino acid that is identical to the amino acid being substituted except that a functional group in the side chain is functionalized with a suitable protecting group. Suitable protecting groups are described in Green and Wuts, *"Protecting Groups in Organic Synthesis"*, John Wiley and Sons, Chapters 5 and 7, 1991, the teachings of which are incorporated herein by reference. As with N-terminal and C-terminal protecting group, preferred protecting groups are those which facilitate transport of the peptide into a cell, for example, by reducing the hydrophilicity and increasing the lipophilicity of the peptide, and which can be cleaved *in vivo,* either by hydrolysis or enzymatically, inside the cell. (Ditter *et al., J. Pharm. Sci. 57:*783 (1968); Ditter *et al., J. Pharm. Sci. 57:*828 (1968); Ditter *et al., J. Pharm. Sci. 58:*557 (1969); King *et*

*al., Biochemistry 26:*2294 (1987); Lindberg *et al., Drug Metabolism and Disposition 17:*311 (1989); and Tunek *et al., Biochem. Pharm. 37:*3867 (1988), Anderson *et al., Arch. Biochem. Biophys. 239:*538 (1985) and Singhal *et al., FASEB J. 1:*220 (1987)). Hydroxyl protecting groups include esters, carbonates and carbamate protecting groups. Amine protecting groups include alkoxy and aryloxy carbonyl groups, as described above for N-terminal protecting groups. Carboxylic acid protecting groups include aliphatic, benzylic and aryl esters, as described above for C-terminal protecting groups. In one embodiment, the carboxylic acid group in the side chain of one or more glutamic acid or aspartic acid residue in a peptide of the present invention is protected, preferably with a methyl, ethyl, benzyl or substituted benzyl ester, more preferably as a benzyl ester.

Provided below are groups of naturally occurring and modified amino acids in which each amino acid in a group has similar electronic and steric properties. Thus, a conservative substitution can be made by substituting an amino acid with another amino acid from the same group. It is to be understood that these groups are non-limiting, i.e. that there are additional modified amino acids which could be included in each group.

Group I includes leucine, isoleucine, valine, methionine, phenylalanine, serine, cysteine, threonine and modified amino acids having the following side chains: ethyl, *n*-butyl, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CHOHCH_3$ and $-CH_2SCH_3$. Preferably, Group I includes leucine, isoleucine, valine and methionine.

Group II includes glycine, alanine, valine, serine, cysteine, threonine and a modified amino acid having an ethyl side chain. Preferably, Group II includes glycine and alanine.

Group III includes phenylalanine, phenylglycine, tyrosine, tryptophan, cyclohexylmethyl, and modified amino residues having substituted benzyl or phenyl side chains. Preferred substituents include one or more of the

following: halogen, methyl, ethyl, nitro, methoxy, ethoxy and -CN. Preferably, Group III includes phenylalanine, tyrosine and tryptophan.

Group IV includes glutamic acid, aspartic acid, a substituted or unsubstituted aliphatic, aromatic or benzylic ester of glutamic or aspartic acid (e.g., methyl, ethyl, *n*-propyl *iso*-propyl, cyclohexyl, benzyl or substituted benzyl), glutamine, asparagine, CO-NH-alkylated glutamine or asparagine (e.g., methyl, ethyl, *n*-propyl and *iso*-propyl) and modified amino acids having the side chain $-(CH_2)_3-COOH$, an ester thereof (substituted or unsubstituted aliphatic, aromatic or benzylic ester), an amide thereof and a substituted or unsubstituted N-alkylated amide thereof. Preferably, Group IV includes glutamic acid, aspartic acid, glutamine, aspargine, methyl aspartate, ethyl aspartate, benzyl aspartate and methyl glutamate, ethyl glutamate and benzyl glutamate.

Group V includes histidine, lysine, arginine, N-nitroarginine, β-cycloarginine, g-hydroxyarginine, N-amidinocitruline and 2-amino-4-guanidinobutanoic acid, homologs of lysine, homologs of arginine and ornithine. Preferably, Group V includes histidine, lysine, arginine, and ornithine. A homolog of an amino acid includes from 1 to about 3 additional methylene units in the side chain.

Group VI includes serine, threonine, cysteine and modified amino acids having C1-C5 straight or branched alkyl side chains substituted with -OH or -SH. Preferably, Group VI includes serine, cysteine or threonine.

In another aspect, suitable substitutions for amino acid residues in the sequence of an αD region or a subsequence of an αD region include "severe" substitutions which result in peptide derivatives which modulate the activity of a PK. Severe substitutions which result in peptide derivatives that modulate the activity of a PK are much more likely to be possible in positions which are not highly conserved

throughout the family of protein kinases than at positions which are highly conserved. Figure 2 shows the consensus sequences of the fifteen to forty amino acids of the αD region of PKs. Positions which are highly conserved among the PK family and the conserved amino acids generally found in those positions have been indicated. Because D-amino acids have a hydrogen at a position identical to the glycine hydrogen side-chain, D-amino acids or their analogs can often be substituted for glycine residues.

A "severe substitution" is a substitution in which the substituting amino acid (naturally occurring or modified) has significantly different size, configuration and/or electronic properties compared with the amino acid being substituted. Thus, the side chain of the substituting amino acid can be significantly larger (or smaller) than the side chain of the amino acid being substituted and/or can have functional groups with significantly different electronic properties than the amino acid being substituted. Examples of severe substitutions of this type include the substitution of phenylalanine or cycohexylmethyl glycine for alanine, isoleucine for glycine, a D amino acid for the corresponding L amino acid or -NH-CH[(-CH_2)$_5$-COOH]-CO- for aspartic acid. Alternatively, a functional group may be added to the side chain, deleted from the side chain or exchanged with another functional group. Examples of severe substitutions of this type include adding an amine or hydroxyl, carboxylic acid to the aliphatic side chain of valine, leucine or isoleucine, exchanging the carboxylic acid in the side chain of aspartic acid or glutamic acid with an amine or deleting the amine group in the side chain of lysine or ornithine. In yet another alternative, the side chain of the substituting amino acid can have significantly different steric and electronic properties from the functional group of the amino acid being substituted. Examples of such modifications include tryptophan for glycine, lysine for aspartic acid and -$(CH_2)_4$COOH for the side chain of serine. These examples are not meant to be limiting.

"Peptidomimetics" can be substituted for amino acid residues in the peptides of this invention. These peptidomimetics replace amino acid residues or act as spacer groups within the peptides. The peptidomimetics often have steric, electronic or configurational properties similar to the replaced amino acid residues but such

similarities are not necessarily required. The only restriction on the use of peptidomimetics is that the peptides retain their protein kinase modulating activity. Peptidomimetics are often used to inhibit degradation of the peptides by enzymatic or other degradative processes. The peptidomimetics can be produced by organic synthetic techniques. Examples of suitable peptidomimetics include tetrazol (Zabrocki *et al., J. Am. Chem. Soc. 110*, 5875-5880 (1988)); isosteres of amide bonds (Jones *et al., Tetrahedron Lett. 29,* 3853-3856 (1988)); LL-3-amino-2-propenidone-6-carboxylic acid (LL-Acp) (Kemp *et al., J. Org. Chem. 50,* 5834-5838 (1985)). Similar analogs are shown in Kemp *et* al., *Tetrahedron Lett. 29,* 5081-5082 (1988) as well as Kemp *et al., Tetrahedron Lett. 29,* 5057-5060 (1988), Kemp *et al., Tetrahedron Lett. 29,* 4935-4938 (1988) and Kemp *et al., J. Org. Chem.54;* 109-115 (1987). Other suitable peptidomimetics are shown in Nagai and Sato, *Tetrahedron Lett. 26,* 647-650 (1985); Di Maio *et al., J. Chem. Soc. Perkin Trans.,* 1687 (1985); Kahn *et al., Tetrahedron Lett. 30,* 2317 (1989); Olson *et al., J. Am. Chem. Soc. 112,* 323-333 (1990); Garvey *et al., J. Org. Chem. 56,* 436 (1990). Further suitable peptidomimetics include hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (Miyake *et al., J. Takeda Res. Labs 43,* 53-76 (1989)); 1,2,3,4-tetrahydroisoquinoline-3-carboxylate (Kazmierski *et al., J. Am. Chem. Soc. 133,* 2275-2283 (1991)); histidine isoquinolone carboxylic acid (HIC) (Zechel *et al., Int. J. Pep. Protein Res. 43* (1991)); (2S, 3S)-methyl-phenylalanine, (2S, 3R)-methyl-phenylalanine, (2R, 3S)-methyl-phenylalanine and (2R, 3R)-methyl-phenylalanine (Kazmierski and Hruby, *Tetrahedron Lett.* (1991)).

The amino acid residues of the peptides can be modified by carboxymethylation, acylation, phosphorylation, glycosylation or fatty acylation. Ether bonds can be used to join the serine or threonine hydroxyl to the hydroxyl of a sugar. Amide bonds can be used to join the glutamate or aspartate carboxyl groups to an amino group on a sugar (Garg and Jeanloz, *Advances in Carbohydrate Chemistry and Biochemistry,* Vol. 43, Academic Press (1985); Kunz, *Ang. Chem. Int.* Ed. English *26*, 294-308 (1987)). Acetal and ketal bonds can also be formed between amino acids and carbohydrates. Fatty acid acyl derivatives can be made, for example, by free amino group (e.g., lysine) acylation (Toth *et al., Peptides: Chemistry,*

Structure and Biology, Rivier and Marshal, eds., ESCOM Publ., Leiden, 1078-1079 (1990)).

Examples of PKs whose activity can be modulated by peptide and peptide derivatives, as described herein, include, but are not limited to, PKs belonging to the following PK families: polo family (Glover *et al., J. Cell Biol., 135:*1681 (1996)), Raf (Pritchard *et al., Nat. Genet. 16:*214 (Jul 1997)), mitogen-activated protein kinases (MAP kinases), Akt/PKB (Frank *et al., Cell 88:*435 (1997) and Hemmings *et al., Science 275:*628 (1997)), G protein-coupled receptor kinases (Premont *et al., FASEB J. 9:*175 (Feb 1995)), Casein kinases, HGF receptors (Boros, *The Lancet 345:*293 (Feb 1995)), Cyclin-Dependent kinases, PDGF receptors, NGF receptors, Jak kinases, NFkB inhibitor kinases (Maniatis, *Science 278:*818 (Oct 1997)), Activin receptors, TGFb receptors, Discoidin domain receptors (Vogel *et al., Molec. Cell. Biol. 1:*13 (Dec 1997)), Src, EGF-R, FGF-R, VEGF-R, HGF-R, PDGF-R, the insulin receptor family and the neurotrophin receptor family. Suitable members of the Polo family include, but are not limited to, Plk, Plx1, polo, SNK, CDC5, Sak, Prk, Fnk, Plo1. Suitable members of the Src family include, but are not limited to, c-Src, c-Yes, FYN, FGR, HCK, LYN, LCK and BLK. Suitable members of the EGF-R family include, but are not limited to EGFR, ErbB2, ErbB3 and ErbB4. Suitable members of the FGF-R family include, but are not limited to FGFR1, FGFR2, FGFR3 and FGFR4. Suitable members of the VEGF-R family include, but are not limited to, Flt1, Flt4 and Flk1. Suitable members of the insulin receptor family include, but are not limited to, INS-R, IRR and IGF1-R. Suitable members of the HGF receptor family include, but are not limited to, c-Met, c-Sea and Ron. Other suitable PKs include, but are not limited to, cyclic AMP (cAMP) dependent protein kinase, protein kinase C, calmodulin dependent kinase, glycogen synthase kinase-3 (GSK3) and cyclic GMP (cGMP) dependent protein kinase, RET (Pasini *et al., TIG 12(4):*138 (Apr 1996)), CSK, Matk, c-Abl, FAK (Frisch *et al., J. Cell. Biol. 134(3):*793 (Aug 1996)), MARK1, 2 and P78 (Drewes *et al., Cell 89:*297 (Apr 1997)), Tie and Tek, Syk and Zap70 (Arpaia *et al., Cell 76:*947 (1994)), Iak1, Chk1 (Sanchez *et al., Science 277:*1497 (Sept 1997)), DAPK, ILK (Hannigan *et al., Nature 379:*91 (Jan 1996)) and JNK.

As shown in Figure 1, the sequences of suitable peptide members of the αD region of PKs from different families include, but are not limited to:

c-Raf (SEQ ID NO. 1); Araf (SEQ ID NO. 2); Braf (SEQ ID NO. 3); cyclic AMP dependent protein kinases a, b and g (cAPK) (SEQ ID NO. 4 to 5); protein kinase C alpha through theta (PKC) (SEQ ID NO. 6 to 12); Akt 1 and 2 (also called Rac α and β) (SEQ ID NO. 13); glycogen synthase kinase α and β (GSK3) (SEQ ID NO. 14 to 15); casein kinases type II α and α' (CK) (SEQ ID NO. 16 to 17); G-receptor coupled protein kinases β-2 adrenergic receptor kinases 1 and 2 (bARK1, 2) (SEQ ID NO. 18); G-protein coupled receptor kinases GRK1 and GRK4 through GRK6 (SEQ ID NO. 19 to 22); calmodulin dependent kinases types I and II a, b, c and d (CaMK) (SEQ ID NO. 23 to 24); members of the Polo-associated family: Plk, Plx1, polo, SNK, CDC5, Sak, Prk, Fnk, Plo1 (SEQ ID NO. 25 to 32); MARK1 and MARK2 and p78 (SEQ ID NO. 33 to 34); cyclin dependent kinases 2, 4 and 6 (SEQ ID NO. 35 to 37); Src, Yes, Fyn, Fgr, Lyn, Hck, Lck (SEQ ID NO. 38 to 44); Csk and Matk (SEQ ID NO. 45 to 46); focal adhesion kinase (FAK) (SEQ ID NO. 47); c-Abl (SEQ ID NO. 48); endothelial growth factor receptors Tie, Tek, FGF receptor (Flg, Bek, FGFR3, FGFR4), PDGF receptor α and β, Flt 1 and 4 and Flk1 (SEQ ID NO. 49 to 59); HGF receptors c-Met, c-Sea and Ron (SEQ ID NO. 60 to 62); EGF receptor (EGFR, ErbB2, ErbB3, ErbB4) (SEQ ID NO. 63 to 66); Ret (SEQ ID NO. 67); NGF receptors (Trk) (SEQ ID NO. 68 to 70); Syk and Zap70 (SEQ ID NO. 71 to 72); Jak kinases 1 through 3 and Tyk2 (SEQ ID NO. 73 to 76); Iak1 (SEQ ID NO. 77); Chk1 (SEQ ID NO. 78); NFkB inhibitor kinases IKK1 and IKK2 (SEQ ID NO. 79 to 80); death associated protein kinase (DAPK) (SEQ ID NO. 81); insulin receptor kinase (IRK) (SEQ ID NO. 82); TGFβ receptor type II (SEQ ID NO. 83); Activin receptor type II A and B (ACTR) (SEQ ID NO. 84 to 85); Activin receptor-like kinases 1 through 6 (ALK1, 2, 3, 4, 5, 6) (SEQ ID NO. 86 to 90); discoidin domain receptor 1 (DDR) and Tyro10 (SEQ ID NO. 91 to 92); ILK (SEQ ID NO. 93); Jun kinase (JNK) (SEQ ID NO. 94).

The amino acid at the N-terminus of the αD region is at position 1 and can be referred to as "$[AA]_1$". The next amino acid in the sequence, referred to as "$[AA]_2$", is at position 2 and is followed by amino acids $[AA]_3$ through $[AA]_m$, which are at

positions 3 to m, where m is the position number of the amino acid at the C-terminus of the αD region. Likewise, (m-12) is the position number of the amino acid twelve amino acid residues before the C-terminus of the αD region. Thus, a peptide 20-mer with an amino acid sequence $[AA]_1$ through $[AA]_{20}$ includes the first twenty amino acids in the αD region. A peptide derivative of the αD region with an amino acid sequence $[AA]_5$ through $[AA]_{16}$ includes the fifth amino acid through the sixteenth amino acid in the αD region, and a peptide derivative of the αD region with an amino acid sequence $[AA]_{(m-12)}$ through $[AA]_m$ includes the last twelve amino acids in the αD region. In this invention, m can have a value between 15 and 45.

The present invention includes peptides having amino acid sequences corresponding to the sequence found in the αD region of PKs, subsequences thereof and modified subsequences thereof. Examples of suitable subsequences include, but are not limited to, sequences corresponding to $[AA]_1$ through $[AA]_m$, $[AA]_1$ through $[AA]_{12}$, $[AA]_5$ through $[AA]_{16}$, $[AA]_9$ through $[AA]_{20}$, $[AA]_{(m-12)}$ through $[AA]_m$, $[AA]_{(m-12)}$ through $[AA]_{(m-2)}$ and $[AA]_{(m-20)}$ through $[AA]_{(m-8)}$ of the αD region of a PK, and subsequences thereof. The above designated sequences are preferred.

The present invention includes peptides having amino acid sequences corresponding to a modified sequence or subsequence of the αD region of PKs and which modulate the activity of PKs including:

Akt1/Raca; ALK1; Braf; c-Abl; c-Met; c-Raf; c-Sea; c-Src; CDK2; CDK4; CDK6; Chk1; CK IIa; Csk; Fak; FGFR-3; Flk1; GSK3b; Hck; Iak1; IKK-1; IKK2; ILK; IRK; Jak1; Jak2; Jak3; Lck; Lyn; MARK1; PDGFR-b; PKCb; Plk; Ret; Ron; SNK; Syk; TGFbRII; TrkB; and Zap70.

In one aspect, one, two or more of the amino acids in the sequence or subsequence are modified with conservative substitutions; the substitutions can be in consensus positions, in non-consensus positions or in both. In another aspect, one, two or more of the amino acids in the sequence or subsequence are modified with severe substitutions; the substitutions are preferably in non-consensus positions. Figure 2 provides examples of conservative amino acid substitutions for the αD region of:

c-Raf (SEQ ID NO. 1); Araf (SEQ ID NO. 2); Braf (SEQ ID NO. 3); cyclic AMP dependent protein kinases a, b and g (cAPK) (SEQ ID NO. 4 to 5); protein kinase C alpha through theta (PKC) (SEQ ID NO. 6 to 12); Akt 1 and 2 (also called Rac α and β) (SEQ ID NO. 13); glycogen synthase kinase α and β (GSK3) (SEQ ID NO. 14 to 15); casein kinases type II α and α' (CK) (SEQ ID NO. 16 to 17); G-receptor coupled protein kinases β-2 adrenergic receptor kinases 1 and 2 (bARK1, 2) (SEQ ID NO. 18); G-protein coupled receptor kinases GRK1 and GRK4 through GRK6 (SEQ ID NO. 19 to 22); calmodulin dependent kinases types I and II a, b, c and d (CaMK) (SEQ ID NO. 23 to 24); members of the Polo-associated family: Plk, Plx1, polo, SNK, CDC5, Sak, Prk, Fnk, Plo1 (SEQ ID NO. 25 to 32); MARK1 and MARK2 and p78 (SEQ ID NO. 33 to 34); cyclin dependent kinases 2, 4 and 6 (SEQ ID NO. 35 to 37); Src, Yes, Fyn, Fgr, Lyn, Hck, Lck (SEQ ID NO. 38 to 44); Csk and Matk (SEQ ID NO. 45 to 46); focal adhesion kinase (FAK) (SEQ ID NO. 47); c-Abl (SEQ ID NO. 48); endothelial growth factor receptors Tie, Tek, FGF receptor (Flg, Bek, FGFR3, FGFR4), PDGF receptor α and β, Flt 1 and 4 and Flk1 (SEQ ID NO. 49 to 59); HGF receptors c-Met, c-Sea and Ron (SEQ ID NO. 60 to 62); EGF receptor (EGFR, ErbB2, ErbB3, ErbB4) (SEQ ID NO. 63 to 66); Ret (SEQ ID NO. 67); NGF receptors (Trk) (SEQ ID NO. 68 to 70); Syk and Zap70 (SEQ ID NO. 71 to 72); Jak kinases 1 through 3 and Tyk2 (SEQ ID NO. 73 to 76); Iak1 (SEQ ID NO. 77); Chk1 (SEQ ID NO. 78); NFkB inhibitor kinases IKK1 and IKK2 (SEQ ID NO. 79 to 80); death associated protein kinase (DAPK) (SEQ ID NO. 81); insulin receptor kinase (IRK) (SEQ ID NO. 82); TGFβ receptor type II (SEQ ID NO. 83); Activin receptor type II A and B (ACTR) (SEQ ID NO. 84 to 85); Activin receptor-like kinases 1 through 6 (ALK1, 2, 3, 4, 5, 6) (SEQ ID NO. 86 to 90); discoidin domain receptor 1 (DDR) and Tyro10 (SEQ ID NO. 91 to 92); ILK (SEQ ID NO. 93); Jun kinase (JNK) (SEQ ID NO. 94). The conservative substitutions can occur by exchanging amino acids with aligned αD region sequences, as shown in Figure 2, as well as by substituting the listed amino acids that are not associated with a known αD region sequence.

Specific examples of peptide derivatives of the present invention include peptides:

Akt1/Raca K014D001; ALK1 K048D101; Braf K003D001 K003D101; c-Abl K061D101; c-Met K073D101; c-Raf K001D101 K001D001; c-Sea K074D101; c-Src K051D101 K051D001; CDK2 K049D101 K049D001; CDK4 K050D001 K050D101; CDK6 K089D101; Chk1 K088D102 K088D101; CK IIα K022D001 K022D101; Csk K058D101 K058D001; Fak K060D101; FGFR-3 K071D101 K071D001 K071D102 K071D901; Flk1 K068D102 K068D101 K068D001 K068d901; GSK3ß K018D003 K018D002 K018D101 K018D001; Hck K056D101; Iak1 K087D101; IKK-1 K090D101; IKK2 K091D101; ILK K107D101 K107D901; IRK K094D001 K094D101 K094D102 K094D103 K094D104; Jak1 K084D101K084D102; Jak2 K085D102 K085D105; Jak3 K086D101 K086D102 K086D103; Lck K057D001 K057D101; Lyn K055D101; MARK1 K045D101; PDGFR-b K064D001 K064D101; PKCß K008D101 K008D001; Plk K035D001 K035D101 K035D102; Ret K080D101 K080D001; Ron K075D101; SNK K038D101; Syk K082D101; TGFβRII K093D101; TrkB K102D101 K102D106 K102D107 K102D108 K102D109; Zap70 K083D101 (SEQ ID NO: 95 to 170, respectively), as specified in Fig.3.

The N-terminus and/or C-terminus of these peptides can be modified, as described above and as shown in Fig. 3. The N-terminal of these peptides is acetylated, stearylated or myristylated and the C-terminal is amidated. Other protecting groups for amides and carboxylic acids can be used, as described above. Optionally, one or both protecting groups can be omitted. The peptides may be linear or cyclic.

Also included are peptides having the sequence of:

Akt1/Raca K014D001; ALK1 K048D101; Braf K003D001 K003D101; c-Abl K061D101; c-Met K073D101; c-Raf K001D101 K001D001; c-Sea K074D101; c-Src K051D101 K051D001; CDK2 K049D101 K049D001; CDK4 K050D001 K050D101; CDK6 K089D101; Chk1 K088D102 K088D101; CK IIα K022D001 K022D101; Csk K058D101 K058D001; Fak K060D101; FGFR-3 K071D101 K071D001 K071D102 K071D901; Flk1 K068D102 K068D101 K068D001 K068d901; GSK3ß K018D003 K018D002 K018D101 K018D001; Hck K056D101; Iak1 K087D101; IKK-1 K090D101; IKK2 K091D101; ILK K107D101

K107D901; IRK K094D001 K094D101 K094D102 K094D103 K094D104; Jak1 K084D101 K084D102; Jak2 K085D102 K085D105; Jak3 K086D101 K086D102 K086D103; Lck K057D001 K057D101; Lyn K055D101; MARK1 K045D101; PDGFR-b K064D001K064D101; PKCß K008D101 K008D001; Plk K035D001 K035D101 K035D102; Ret K080D101 K080D001; Ron K075D101; SNK K038D101; Syk K082D101; TGFβRII K093D101; TrkB K102D101 K102D106 K102D107 K102D108 K102D109; Zap70 K083D101 (SEQ ID NO: 95 to 170, respectively), as specified in Fig.3, with the proviso that any one or two of the amino residues in the peptide can vary, being replaced by any naturally occurring amino acid or analog thereof.

The present invention also includes cyclic peptides having amino acid sequences corresponding to a modified sequence or subsequence of the αD region of PKs. These cyclic peptides modulate the activity of PKs.

A "cyclic peptide" refers, for example, to a peptide or peptide derivative in which a ring is formed by the formation of a peptide bond between the nitrogen atom at the N-terminus and the carbonyl carbon at the C-terminus.

"Cyclized" also refers to the forming of a ring by a covalent bond between the nitrogen at the N-terminus of the compound and the side chain of a suitable amino acid in the peptide, preferably the side chain of the C-terminal amino acid. For example, an amide can be formed between the nitrogen atom at the N-terminus and the carbonyl carbon in the side chain of an aspartic acid or a glutamic acid. Alternatively, the peptide or peptide derivative can be cyclized by forming a covalent bond between the carbonyl at the C-terminus of the compound and the side chain of a suitable amino acid in the peptide, preferably the chain of the N-terminal amino acid. For example, an amide can be formed between the carbonyl carbon at the C-terminus and the amino nitrogen atom in the side chain of a lysine or an ornithine. Additionally, the peptide or peptide derivative can be cyclized by forming an ester between the carbonyl carbon at the C-terminus and the hydroxyl oxygen atom in the side chain of a serine or a threonine.

"Cyclized" also refers to forming a ring by a covalent bond between the side chains of two suitable amino acids in the peptide, preferably the side chains of the

two terminal amino acids. For example, a disulfide can be formed between the sulfur atoms in the side chains of two cysteines. Alternatively, an ester can be formed between the carbonyl carbon in the side chain of, for example, a glutamic acid or an aspartic acid, and the oxygen atom in the side chain of, for example, a serine or a threonine. An amide can be formed between the carbonyl carbon in the side chain of, for example, a glutamic acid or an aspartic acid, and the amino nitrogen in side chain of, for example, a lysine or an ornithine.

In addition, a peptide or peptide derivative can be cyclized with a linking group between the two termini, between one terminus and the side chain of an amino acid in the peptide or peptide derivative, or between the side chains to two amino acids in the peptide or peptide derivative. Suitable linking groups are disclosed in Lobl *et al.*, WO 92/00995 and Chiang *et al.*, WO 94/15958, the teachings of which are incorporated into this application by reference.

Suitable substitutions in the original amino acid sequence or subsequence are those which result in a peptide derivative, as defined above, which modulates the activity of a PK. The activity of a PK is "modulated" when the activity of the PK is increased or decreased. An increase or decrease in the activity of a PK can be detected by assessing *in vitro* the extent of phosphorylation of a protein substrate of the PK being tested or by a corresponding modulation, increase or decrease, in a cellular activity or function which is under the control of the PK. Examples of these cellular functions include cell proliferation, cell differentiation, cell morphology, cell survival or apoptosis, cell response to external stimuli, gene expression, lipid metabolism, glycogen or glucose metabolism and mitosis.

It can be readily determined whether a peptide or peptide derivative modulates the activity of a PK by incubating the peptide or peptide derivative with cells which have one or more cellular activities controlled by a PK. The cells are incubated with the peptide or peptide derivative to produce a test mixture under conditions suitable for assessing the activity of the protein kinase. The activity of the PK is assessed and compared with a suitable control, e.g., the activity of the same cells incubated under the same conditions in the absence of the peptide or peptide derivative. A greater or

lesser activity of the PK in the test mixture compared with the control indicates that the test peptide or peptide derivative modulates the activity of the PK.

Suitable cells for the assay include normal cells which express a membrane bound or intracellular PK, cells which have been genetically engineered to express a PK, malignant cells expressing a PK or immortalized cells which express a PK.

Conditions suitable for assessing PK activity include conditions suitable for assessing a cellular activity or function under control of the PK. Generally, a cellular activity or function can be assessed when the cells are exposed to conditions suitable for cell growth, including a suitable temperature (for example, between about 30 °C to about 42 °C) and the presence of the suitable concentrations of nutrients in the medium (e.g., amino acids, vitamins, growth factors).

In another aspect, the activity of certain PK (e.g., Atk/PKB, Dudek *et al., Science 275*:661 (1997)) can be evaluated by growing the cells under serum deprivation conditions. Cells are typically grown in culture in the presence of a serum such as bovine serum, horse serum or fetal calf serum. Many cells, for example, nerve cells such as PC-12 cells, generally do not survive with insufficient serum. The use of insufficient serum to culture cells is referred to as "serum deprivation conditions" and includes, for example, from 0% to about 4% serum. PK activity is determined by the extent to which a peptide or peptide derivative can protect cells, e.g., neuronal cells, from the consequences of serum deprivation. Specific conditions are provided in Dudek *et al.*, and in Example 4 of co-pending and concurrently filed application entitled "SHORT PEPTIDES WHICH SELECTIVELY MODULATE INTRACELLULAR SIGNALLING" (filed on May 21, 1997, U.S. Application Serial No. 08/861,153), the teachings of which are incorporated herein by reference.

Generally, the activity of the PK in the test mixture is assessed by making a quantitative measure of the cellular activity which the PK controls. The cellular activity can be, for example, cell proliferation. Examples of cells in which proliferation is controlled by a PK include endothelial cells such as bovine aortic cells, mouse MSI cells or mouse SVR cells (see Arbiser *et al., Proc. Natl. Acad. Sci. USA 94*:861 (1997)), vascular smooth muscle cells, and malignant cells of various

tissues such as breast cancer, lung cancer, colon cancer, prostate cancer or melanoma. PK activity is assessed by measuring cellular proliferation, for example, by comparing the number of cells present after a given period of time with the number of cells originally present. One example of PKs having to do with cellular proliferation is the polo family and the CDKs.

Specific examples of conditions suitable for determining the activity of PKs by assessing cell proliferation are provided in Example 2.

If cells are being used in which the PK controls cell differentiation (e.g., preadipocytes such as 3T3-L1 expressing PKs Akt/PKB, GSK3 and protein kinase A - see Kohn *et al., J. Biol. Chem. 271:*31372 (1996)), activity is assessed by measuring the degree of differentiation. Activity can be assessed by changes in the metabolic activity of cells such as primary adipocytes, hepatocytes and fibroblasts by measuring changes in glucose uptake, lipogenesis, or glycogen metabolism (see, for example, Weise *et al., J. Biol. Chem. 270:*3442 (1995)). Activity can also be assessed by the extent to which gene expression, cell morphology or cellular phenotype is altered (e.g., the degree to which cell shape is altered or the degree to which the cells assume a spindle-like structure). One example of a change in cellular morphology is reported in the co-pending and concurrently filed application entitled "SHORT PEPTIDES WHICH SELECTIVELY MODULATE INTRACELLULAR SIGNALLING" (filed on May 21, 1997, U.S. Application Serial No. 08/861,153), which discloses that certain peptide derivatives of the HJ loop of protein tyrosine kinases can cause vascular smooth muscle cells to become elongated and assume a spindle-like shape.

It is to be understood that the assay described hereinabove for determining whether a peptide or peptide derivative modulates a cellular activity or function under the control of a PK can be performed with cells other than those specifically described herein. PKs not yet discovered or PKs whose function is not yet known can also be used in this assay, once it has been determined which cellular functions or activities they control. These PKs are also within the scope of the present invention.

The present invention is also directed to a method of modulating the activity of a protein kinase in a subject. A "subject" is preferably a human, but can also be animals in need of treatment, e.g., veterinary animals (e.g., dogs, cats, and the like),

farm animals (e.g., cows, pigs, horses and the like) and laboratory animals (e.g., rats, mice, guinea pigs and the like).

The activity of a PK in a subject can be modulated for the purpose of treating diseases that are caused by over activity or under activity of PKs. For example, MAP kinases (Seger and Krebs, *FASEB J. 9:*726 (1995)) and cyclin dependent protein kinases ("Molecular Biology of the Cell," Alberts, Bray, Lewis, Raff, Roberts and Watson, eds. Chapter 5, (Garland Publishing, Inc.), (1994)), are central components of the cell-division cycle control system in eukaryotic cells. Other PKs, for example, protein kinase C and Raf kinases (Nishizuka, *The FASEB Journal 9:*484 (1995), Locric, *et al., Oncogene 12:*1109 (1996) and Laird *et al., J. Biol. Chem. 270:*26,742 (1995)) are, in turn, involved in the control of MAP kinases or are activated during mitosis. The G protein-coupled receptor kinases (GRKs), on the other hand, desensitize the receptors and are thereby involved in the regulation of various hormonal responses (Freedman and Lefkowitz, *Recent Prog. Hormon. Res. 51:*319 (1996). Activation of Akt/PKB is implicated in the inhibition of apoptosis, i.e., programmed cell death (Frank *et al., Cell 88:*435 (1997) and Hemmings *Science 275:*628 (1997)). Peptides and peptide derivatives of the present invention which modulate the activity of these enzymes can be used to treat cancer in a subject when administered to the subject in a therapeutically effective amount.

c-AMP dependent kinase, GSK3 and Akt/PKB are involved in the control of glycogen metabolism. Peptide and peptide derivatives of the present invention which modulate the activity of cAMP dependent kinase can be used to treat Type II diabetes and hemorrhagic shock in a subject when administered to the subject in a therapeutically effective amount. cAMP derivatives have also been reported to inhibit the growth of human cancer cells (*Katsros et al., FEBS Lett. 223:*97 (1987)), indicating that inhibitors of cAMP dependent kinases can also be useful in the treatment of cancer.

Raf kinases are involved in the control of lipid metabolism. Peptide and peptide derivatives of the present invention which modulate the activity of Raf kinases can be used to treat obesity in a subject when administered to the subject in a therapeutically effective amount.

Agents which modulate the activity of protein kinase C can be used to treat a wide variety of other disease conditions, including cardiovascular diseases (e.g., thrombosis, atherosclerosis, arteriosclerosis, cardiac hypertrophy, ischemia, reperfusion injury and hypertension), immunosuppressive and inflammatory disorders (e.g., asthma, psoriasis, systemic lupus erythematous, diabetes mellitus, suppression of organ transplant rejection, multiple sclerosis, inflammatory bowel disease and AIDS), central nervous system diseases (e.g., Alzheimer's disease, stroke and trauma), septic shock based on protein kinase C activation and ischemia induced renal failure (Nambi, WO 93/16703, Bradshaw, *et al., Agents Action 38:*135 (1993) and Birchall *et al., The J. Pharm. and Exper. Therapeut. 2:*922 (1994)). Peptide and peptide derivatives of the present invention which modulate the activity of protein kinase C can be used to treat these diseases in a subject when administered to the subject in a therapeutically effective amount.

Phosphorylation by G-protein receptor kinases are known (Freedman and Lefkowitz, *Recent Prog. Hormon. Res. 51:*319 (1996)) to result in receptor desensitization, thereby extending the duration of hormonal effects of, for example, adrenalin. Thus, agents which modulate the activity of G-protein receptor kinases can be used in the treatment of disease resulting from a lower bioavailability of the corresponding ligand, such as dopamine. Inhibitors of calmodulin dependent kinases have been reported to inhibit dopamine release (Nagatsu *et al., Biochem. Biophys. Research, Commun. 143:*1045 (1987)). Thus, agents which modulate the activity of G-protein receptor kinases and calmodulin receptor kinases can be useful in the treatment of diseases involving dysfunction of dopamine signalling, for example, Parkinson's Disease. Inhibitors of calmodulin dependent kinases have also been reported to relax arterial muscle (Saitoh *et al., J. Bio. Chem. 262:*7796 (1987)) and therefore can be used in treating hypertension. Inhibition of GSK3 might increase the intracellular activity of the insulin receptor and thereby enhance glucose uptake and other related metabolic activities. Thus, agents which modulate the activity of GSK3 can be useful in the treatment of Type I and Type II diabetes.

Cancer can be treated by anti-angiogenic therapies. Inhibition of c-Met or tyrosine kinase receptors which respond to fibroblast growth factor (FGF), or

vascular endothelial growth factor (VEGF) decreases angiogenesis. As a result, cancers can be treated by administering a therapeutically effective amount of a peptide or peptide derivative of the present invention which results in decreased activity of c-Met or tyrosine kinase receptors which respond to FGF or VEGF. In addition, RET is involved in certain thyroid cancers; therapeutically effective amounts of peptides or peptide derivatives of the present invention which modulate the activity of RET can be used to treat these thyroid cancers. Restenosis is caused by vascular smooth muscle proliferation in response to, for example, vascular injury caused by balloon cathaterization. Vascular smooth muscle proliferation is also a cause of arteriosclerosis. Vascular smooth muscle proliferation is a result of, for example, inhibition of Csk and/or stimulation of tyrosine kinase receptors which respond to FGF or platelet derived growth factor (PDGF). Thus, restenosis and arteriosclerosis can be treated with a therapeutically effective amount of a peptide or peptide derivative of the present invention which inhibits tyrosine kinase receptors which respond to FGF or PDGF or which activate Csk.

FGF has also been implicated in psoriasis, arthritis and benign prostatic hypertrophy (Dionne *et al.*, WO 92/00999). These conditions can be treated with αD peptides from PKs which respond to FGF.

Src activity is responsible, at least in part, for bone resorption. Thus, osteoporosis can be treated with a therapeutically effective amount of a peptide or peptide derivative of the present invention which inhibits Src activity or which activates Csk.

Lyn and Hck are activated during the non-specific immune response which occurs in individuals with arthritis which occurs in individuals as a result of allergic responses. Lyn is also activated in individuals with septic shock. Thus, these conditions can be treated with a therapeutically effective amount of a peptide or peptide derivative of the present invention which inhibits the activity of these PKs.

Lck, Jak1and Jak3 are expressed in T cells and are activated during a T cell immune response. Similarly, Lyn is expressed in B cells and activated during a B cell immune response. Thus, conditions which are caused by overactivation of T cells or B cells can be treated by administering a therapeutically effective amount of a

peptide or peptide derivative of the present invention which inhibits Lck, Jak1, Jak3 or Lyn, respectively. Conditions which are caused by underactivation of T cells or B cells can be treated by administering a therapeutically effective amount of a peptide or peptide derivative of the present invention which stimulates Lck, Jak1, Jak3 or Lyn, respectively.

For example, it is now known that functionally polarized responses are displayed by two subpopulations of CD4+ T cells, named Th1 and Th2. Th1 cells produce interferon γ (IFNγ) and tumor necrosis factor β (TNFβ). Th2 cells produce interleukins 4,5,10 and 13 (IL-4, IL-5, IL-10 and IL-13). Thus, Th1 responses are beneficial for protection against intracellular parasites and can aid tumor immunity. Th2, on the other hand, is responsible for strong antibody responses. Several diseases are associated with an overexpression of Th1 or Th2 cells. Examples include Th1 responses which predominate in organ-specific autoimmune diseases, and Th2 responses which are responsible for triggering allergic reactions, including IgE production.

Many of the cytokines involved in Th1/Th2 maturation mediate their signaling through members of the Jak family of intracellular kinases; e.g., IL-4 responses are mediated via Jak1 and Jak3, IFNγ signals are mediated via Jak1 and Jak2. Therefore, a manipulation of the activity of members of the Jak family by αD region derived peptides can modulate Th1/Th2 activities and help boost desired immune responses or aid in alternating pathological responses.

A severe reduction of the B cell progenitor kinase leads to human X-linked agammaglobulinemia, which can be treated by administering a therapeutically effective amount of a peptide or peptide derivative of the present invention which stimulates B cell progenitor kinase. Decreased function of other PKs can also lead to disease. For example, a decrease in the activity of insulin receptor tyrosine kinase (IRK) is a cause of various types of diabetes. These types of diabetes can be treated by administering a therapeutically effective amount of a peptide or peptide derivative of the present invention which increases the activity of IRK. In addition, the viability and proper function of neurons depend on signaling by neurotrophic factors. TrkB, in particular, is implicated in signal transduction of BDNF. Thus, peptides of this

invention that can enhance TrkB kinase activity will be beneficial for a variety of CNS disorders.

Another family of transmembrane protein kinases is composed of members of the TGFβ/Activin/BMP receptors which transduce signals of the corresponding cytokines. The TGFβ/Activin/BMP cytokines participate in processes such as tissue repair, including the induction of bone formation. Therefore, modulation of the activity of these receptor kinases can assist tissue repair, inhibit tissue fibrosis and enhance bone formation.

Based on methods disclosed herein, peptides and peptide derivatives can be designed to modulate the activity of PKs whose αD region has been sequenced or will be sequenced in the future and whose cellular function is known. As a consequence, peptides and peptide derivatives can be designed to affect (increase or decrease) those cellular functions. It is possible that future research will reveal that certain disease conditions, whose underlying causes are presently unknown, are brought about by the overactivity or underactivity of cellular functions controlled by these PKs. These diseases can be treated by administering peptides which are peptide derivatives of the αD region of the overactive or underactive PK. Suitable peptides and peptide derivatives can be identified by methods disclosed herein. These methods of treatment, peptides and peptide derivatives are encompassed within the scope of the present invention.

A "therapeutically effective amount" is the quantity of compound which results in an improved clinical outcome as a result of the treatment compared with a typical clinical outcome in the absence of the treatment. An "improved clinical outcome" results in the individual with the disease experiencing fewer symptoms or complications of the disease, including a longer life expectancy, as a result of the treatment. With respect to cancer, an "improved clinical outcome" includes a longer life expectancy. It can also include slowing or arresting the rate of growth of a tumor, causing a shrinkage in the size of the tumor, a decreased rate of metastasis and/or improved quality of life (e.g., a decrease in physical discomfort or an increase in mobility).

With respect to diabetes, an improved clinical outcome refers to a longer life expectancy, a reduction in the complications of the disease (e.g., neuropathy, retinopathy, nephropathy and degeneration of blood vessels) and an improved quality of life, as described above.

With respect to obesity, an improved clinical outcome refers to increased weight reduction per caloric intake or a reduction in food intake. It also refers to a decrease in the complications which are a consequence of obesity, for example heart disease such as arteriosclerosis and high blood pressure.

The amount of peptide or peptide derivative administered to the individual will depend on the type and severity of the disease and on the characteristics of the individual, such as general health, age, sex, body weight and tolerance to drugs. The skilled artisan will be able to determine appropriate dosages depending on these and other factors. Typically, a therapeutically effective amount of the peptide or peptide derivative can range from about 1 mg per day to about 1000 mg per day for an adult. Preferably, the dosage ranges from about 1 mg per day to about 100 mg per day.

The peptide and peptide derivatives of the present invention are preferably administered parenterally. Parenteral administration can include, for example, systemic administration, such as by intramuscular, intravenous, subcutaneous, or intraperitoneal injection. Peptides or peptide derivatives which resist proteolysis can be administered orally, for example, in capsules, suspensions or tablets. The peptide or peptide derivative can also be administered by inhalation or insufflation or via a nasal spray.

The peptide or peptide derivative can be administered to the individual in conjunction with an acceptable pharmaceutical carrier as part of a pharmaceutical composition for treating the diseases discussed above. Suitable pharmaceutical carriers may contain inert ingredients which do not interact with the peptide or peptide derivative. Standard pharmaceutical formulation techniques may be employed such as those described in Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA. Suitable pharmaceutical carriers for parenteral administration include, for example, sterile water, physiological saline, bacteriostatic saline (saline containing about 0.9% mg/ml benzyl alcohol), phosphate-buffered

saline, Hank's solution, Ringer's-lactate and the like. Methods for encapsulating compositions (such as in a coating of hard gelatin or cyclodextran) are known in the art (Baker, *et al., Controlled Release of Biological Active Agents*, John Wiley and Sons, 1986).

The peptide and peptide derivatives of the present invention have many utilities other than as a therapeutic agent. Some of these uses are discussed in the following paragraphs.

The αD region peptides of the present invention are derived from an array which is linear in the native protein. These peptides can be useful in the preparation of specific antibodies against PKs. Moreover, since the αD region sequence is unique to each sub-family of PK, anti-αD region antibodies can be specifically used to isolate distinct sub-families of PK.

Suitable antibodies can be raised against an αD region peptide by conjugating the peptide to a suitable carrier, such as keyhole limpet hemocyanin or serum albumin; polyclonal and monoclonal antibody production can be performed using any suitable technique. A variety of methods have been described (see e.g., Kohler *et al., Nature, 256:* 495-497 (1975) and *Eur. J. Immunol. 6:* 511-519 (1976); Milstein *et al., Nature 266: 550-552 (1977);* Koprowski *et al.,* U.S. Patent No. 4,172,124; Harlow, E. and D. Lane, 1988, *Antibodies: A Laboratory Manual*, (Cold Spring Harbor Laboratory: Cold Spring Harbor, NY); *Current Protocols In Molecular Biology*, Vol. 2 (Supplement 27, Summer 1994), Ausubel, F.M. *et al.*, Eds., (John Wiley & Sons: New York, NY), Chapter 11, (1991)). Generally, a hybridoma can be produced by fusing a suitable immortal cell line (e.g., a myeloma cell line such as SP2/0) with antibody producing cells. The antibody producing cell, preferably those of the spleen or lymph nodes, can be obtained from animals immunized with the antigen of interest. The fused cells (hybridomas) can be isolated using selective culture conditions, and cloned by limiting dilution. Cells which produce antibodies with the desired specificity can be selected by a suitable assay (e.g., ELISA).

Antibodies, including monoclonal antibodies, against αD region peptides have a variety of uses. For example, those against or reactive with the protein from which the αD peptides was derived, and preferably which bind specifically to said protein,

can be used to identify and/or sort cells exhibiting that protein on the cell surface (e.g., by means of fluorescence activated cell sorting or histological analyses). Monoclonal antibodies specific for the protein can also be used to detect and/or quantitate the protein expressed on the surface of a cell or present in a sample (e.g., in an ELISA). Alternatively, the antibodies can be used to determine if an intracellular PK is present in the cytoplasm of the cell. A lysate of the cell is generated (for example, by treating the cells with sodium hydroxide (0.2 N) and sodium dodecyl sulfate (1%) or with a non-ionic detergent like NP-40, centrifugating and separating the supernatant from the pellet), and treated with anti-αD region antibody specific for the PK. The lysate is then analyzed, for example, by Western blotting or immunoprecipitation for complexes between PK and antibody. Some PKs become membrane-bound or cytoskeleton-associated following stimulation. Anti-αD region antibodies can be utilized for the study of the intracellular distribution (compartmentalization) of various subfamilies of PKs under various physiological conditions via the application of conventional immunocytochemistry such as immunofluorescence, immunoperoxidase technique and immunoelectron microscopy, in conjunction with the specific anti-αD region antibody.

Antibodies reactive with the αD region are also useful to detect and/or quantitate the PK or αD peptide in a sample, or to purify the PK from which the αD region was derived (e.g., by immunoaffinity purification).

The αD region within PKs plays a key role in regulating the activity of PKs, as is evidenced by the fact that the peptides and peptide derivatives of the present invention have such a dramatic effect on the activity of PKs. The αD region peptides of the present invention can also be used to identify ligands which interact with the αD regions of specific PKs and which modulate the activity PKs. For example, an affinity column can be prepared to which a specific αD region peptide is covalently attached, directly or via a linker. This column, in turn, can be utilized for the isolation and identification of specific ligands which bind the αD region peptide and which will also likely bind the PK from which the αD region peptide was derived. The ligand can then be eluted from the column, characterized and tested for its ability to modulate PK function.

Peptide sequences in the compounds of the present invention may be synthesized by solid phase peptide synthesis (e.g., t-BOC or F-MOC) method, by solution phase synthesis, or by other suitable techniques including combinations of the foregoing methods. The t-BOC and F-MOC methods, which are established and widely used, are described in Merrifield, *J. Am. Chem. Soc. 88*:2149 (1963); Meienhofer, *Hormonal Proteins and Peptides,* C.H. Li, Ed., Academic Press, 1983, pp. 48-267; and Barany and Merrifield, in *The Peptides,* E. Gross and J. Meienhofer, Eds., Academic Press, New York, 1980, pp. 3-285. Methods of solid phase peptide synthesis are described in Merrifield, R.B., *Science, 232*: 341 (1986); Carpino, L.A. and Han, G.Y., *J. Org. Chem., 37*: 3404 (1972); and Gauspohl, H. *et al., Synthesis, 5*: 315 (1992)). The teachings of these references are incorporated herein by reference.

Methods of cyclizing compounds having peptide sequences are described, for example, in Lobl *et al.,* WO 92/00995, the teachings of which are incorporated herein by reference. Cyclized compounds can be prepared by protecting the side chains of the two amino acids to be used in the ring closure with groups that can be selectively removed while all other side-chain protecting groups remain intact. Selective deprotection is best achieved by using orthogonal side-chain protecting groups such as allyl (OAI) (for the carboxyl group in the side chain of glutamic acid or aspartic acid, for example), allyloxy carbonyl (Aloc) (for the amino nitrogen in the side chain of lysine or ornithine, for example) or acetamidomethyl (Acm) (for the sulfhydryl of cysteine) protecting groups. OAI and Aloc are easily removed by Pd° and Acm is easily removed by iodine treatment.

The invention is illustrated by the following examples which are not intended to be limiting in any way.

Example 1 - Preparation of αD Peptides

The novel compounds of this invention can be synthesized utilizing a 430A Peptide Synthesizer from Applied Biosystems using F-Moc technology according to manufacturer's protocols. Other suitable methodologies for preparing peptides are known to person skilled in the art. See e.g., Merrifield, R.B., *Science, 232*: 341 (1986); Carpino, L.A., Han, G.Y., *J. Org. Chem., 37*: 3404 (1972); Gauspohl, H., *et*

al., Synthesis, 5: 315 (1992)), the teachings of which are incorporated herein by reference.

Rink Amide Resin [4(2',4' Dimethoxyphenyl-FMOC amino methyl) phenoxy resin] was used for the synthesis of C-amidated peptides. The alpha-amino group of the amino acid was protected by an FMOC group, which was removed at the beginning of each cycle by a weak base, 20% piperidine in N-methylpyrrolidone (NMP). After deprotection, the resin was washed with NMP to remove the piperidine. *In situ* activation of the amino acid derivative was performed by the FASTMOC Chemistry using HBTU (2(1-benzotriazolyl-1-yl)-1,1,3,3-tetramethyluronium) dissolved in HOBt (1-hydroxybenzotriazole) and DMF (dimethylformamide). The amino acid was dissolved in this solution with additional NMP. DIEA (diisopropylethylamine) was added to initiate activation. Alternatively, the activation method of DCC (dicyclohexylcarbodiimide) and HOBt was utilized to form an HOBt active ester. Coupling was performed in NMP. Following acetylation of the N-terminus (optional), TFA (trifluoroacetic acid) cleavage procedure of the peptide from the resin and the side chain protecting groups was applied using 0.75 g crystalline phenol; 0.25 ml EDT (1,2-ethandithiol); 0.5 ml thioanisole; 0.5 ml D.I. H_2O; 10 ml TFA.

Example 2 - αD Peptide Derivatives of Jak3 Modulate Proliferation of Endothelial Cells *In Vitro*

Human endothelial cells (referred to herein as "HEC cells") are the cell line described by Schweitzer *et al., Laboratory Investigation 76(1)*:25 (1997). Human prostate cancer cells (PC3) were obtained by the procedures disclosed in Arbiser *et al., Proc. Natl. Acad. Sci. 94*:861 (1997), the teachings of which are incorporated herein by reference.

96 well, flat bottom, tissue culture microtiter plates were precoated with gelatin (Difco) immediately prior to cell plating by adding 0.100 ml/well of freshly filtered 1% gelatin in glass double distilled water (DDW). The wells were incubated for about 1 hour at 37°C, and then the excess solution was removed by aspiration.

Culture medium was prepared from DMEM, pencillin/ streptomycin/glutamine (penicillin - 100 U/ml; streptomycin - 100 μμg/mL; and glutamine - 2mM) and 10% endotoxin free bovine calf serum (Hyclone). A suspension of the cell type being tested at 25 x 10^3 cells/ml was prepared in the above described culture medium and distributed 0.160 ml/well (about 4000 endothelial cells/well).

A series of αD peptide stock solutions was prepared by diluting a 10 mM solution of the αD peptide in 100% DMSO with phosphate buffered saline (PBS) containing 0.1% BSA. The concentration of αD peptide in each stock solution was adjusted to nine times the desired concentration of the αD peptide in the assay mixture.

0.020 ml of each αD peptide stock solution was added to the corresponding wells about 2 hours after cell plating, with six replicates for each concentration. In addition, BSA solution with no added αD peptide was used as a control. The wells were incubated for 72-80 hours at 37°C in a 10% CO_2 humidified incubator.

The plates were labeled and the medium discarded. Each plate was then washed one time with PBS (0.200 ml/well). The wells were then fixed by washing with 100% ethanol (0.200 ml/well for 5 minutes). The ethanol was removed and the wells dried completely. Alternatively, the wells were fixed with 4% formaldehyde PBS (PBS buffered 10% formalin from Fisher Scientific; Catalog No. HC200-1) (0.12 ml/well) for at least 30 minutes. Fixing with formaldehyde enhances the O.D. compared with ethanol.

The wells were washed one time with borate buffer (0.1 M, pH 8.5). Freshly filtered 1% methylene blue solution (0.600 ml/well) was then added to the wells and incubated for 10 minutes at room temperature. The wells were then washed five times with tap water, after which the wells were dried completely. 0.200 ml/well of 0.1 N HCl was added to extract the color. After extracting overnight, the O.D. was read at 630 nm to determine the number of cells per well. The procedure for counting cells is described in greater detail in Oliver et al., *J. of Cell Sci., 92*:513 (1989), the teachings of which are incorporated herein by reference.

The results for αD peptide K086D101 is shown in Table I.

Table I

Peptide	S.I.* (μM) for HEC Cells	S.I.* (μM) for PC3 Cells
K086D101	0.6	0.6

*Concentration at which significant inhibition of cell proliferation was observed.

As can be determined from the results in Table I, αD peptide derivatives of Jak3 inhibited cell proliferation of human endothelial cells and human prostate cancer cell line PC3.

Example 3 - Appetite Suppression by Jak2-Derived Peptide

Male CB6F1 or C57BL mice (Harlan), about 2-4 months old, were fed a pelleted rodent maintenance diet (Koffolk, Tel Aviv, Israel, 19520). The food containers for each group were weighed daily and the average food consumption was calculated per mouse per day.

During the experimental period, the mice were injected intraperitoneally once a day for two consecutive days, 4mg/mouse, with K085D102 (a Jak2-derived peptide from the αD region) solubilized in 10% DMSO in PBS + 0.1% BSA in a volume of 0.2 ml. The control groups were injected with 0.2 ml of the vehicle only.

Figures 4 and 5 illustrate the results obtained with CB6F1 mice while Table II summarizes the results obtained with C57BL mice.

Table II

		Food Intake (g/mouse/day)				% change in body wt. (relative/to day 0)			
	n	baseline	treatment day 1	treatment day 2	recovery	day 0	treatment day 1	treatment day 2	recovery
Control I	5	3.19	2.88	3.12	4.68	100%	99%	100%	102%
Control II	5	3.68	2.85	4.92	4.5	100%	97%	99%	100%
Experiment	4	3.16	0.24	1.43	3.62	100%	94%	95%	97%

These results demonstrate that peptides from the αD region of Jak2 have a marked effect on food intake and, concomitantly, on body weight. These peptides exhibit appetite suppression properties.

Example 4 - Th1/Th2 Bioassay

$0.5x10^6$ small resting CD4+ T cells were isolated from lymph nodes of 8 week-old Balb/c mice. These CD4+ T cells were incubated for 5 days in 2 ml culture medium in 24 well plates coated with anti-CD3 and anti-CD28 antibodies: (5μg/ml and 2 μg/ml, respectively). 0.4, 2 or 10 μM Jak-derived peptides, initially in 10 μl DMSO, were present in the medium during the 5 day activation period. Control wells contained 10 μl of DMSO (the solvent of the peptide).

At the end of the 5 day stimulation period, the medium was replaced with fresh medium containing 10 u/ml IL-2 and the cells were removed from the antibody-coated wells to uncoated wells for a 3 day "rest" and expansion period. Under these stimulating and rest conditions, the differentiation process led to the acquisition of Th2 phenotype (high IL-4 and low IFNγ production upon secondary challenge).

At the end of the rest period, the cells were removed, washed and counted. $0.5x10^6$ cells were restimulated in 1 ml of culture medium by incubation for 24 hours on anti-CD3- + anti-CD28- coated 24 well plates. At the end of the 24 hour restimulation period, the supernatant was removed and the level of secreted IL-4 and IFNγ was determined by ELISA. The results were expressed as u/ml or pg/ml of IL-4 and IFNγ respectively, which were secreted into the culture medium by $0.5x10^6$ cells during the restimulation period.

Figure 6 depicts an undeniable Th1 conversion of CD4+ T cells incubated in the presence of various concentrations of the Jak3 K086D102 peptide, derived from the αD region. The Th1 conversion is manifested by an increase in IFNγ production and a decrease in IL-4 production. This demonstrates the cell differentiation and induction properties of these αD region peptides.

Example 5 - Glucose Uptake by Adipose Tissue Cells

1. Materials

30 ml plastic bottle (Nalgene 2103-0001)

50 ml plastic conical tube (Miniplast 204-21)

TC tubes (Nunc 146183)

Test tubes (Sarstedt 72.7000)

250 μ nylon mesh

Collagenase Type 1 (Worthington CLS 4196)

Dinonyl phthalate (Merck 1.09669.0100)

3 H-Deoxy Glucose (ICN 27088S.2), 30 Ci/mmole, 0.25 mCi, 0.25 ml

2. Adipose Cell Isolation

Krebs Ringer Bicarbonate HEPES buffer, containing 1% bovine fraction 5 albumin and 200 nM adenosine was made, using stock solutions:

Stock solution 1 - salts

120 mM 35.04 NaCl

4 mM 2.73g KH_2PO_4

1 mM 0.55g $CaCl_2$ (0.74g $CaCl_2 \cdot 2H_2O$) Dissolved in a small flask and added to other salts.

Stock solution 2 - Sodium bicarbonate

10mM 4.2g $NaHCO_3$; dissolved in a 500 ml volumetric flask.

Stock solution 3 - HEPES

30 mM 35.75g HEPES (39.05g HEPES Sodium salt); dissolved in a 500 ml volumetric flask pH to 7.4 before being brought up to volume.

10 ml of each solution (1,2 and 3) was used per 100 ml double distilled water on day of use.

Stock solution 4 - Adenosine (2mM)

To 3ml of buffer with 10 mg collagenase, 3g epididymal fat pad (from 2-3 male rats) was introduced. The fat was cut up with scissors. The pieces of fat were swirled and shaken in a 37°C water bath set at 100-150 repetitions/minute for approximately 1 hour with swirling every 15 minutes while digesting and every 5 minutes towards the end. About 6 ml of buffer was added to the vial.

A 250 μ nylon mesh over the top was secured with a rubber band and the contents of the container were gently squeezed into a 50 ml plastic tube. The total volume for each wash was 15 ml.

The tube was centrifuged. The adipose cells floated to the top of the liquid. The buffer was removed using a 35 ml metal-tipped syringe with a needle. Buffer was added to 15 ml and the clumps of cells were gently broken up by mixing up and down in the syringe. This process was repeated for a total of 4 centrifugations at 1000 with the last centrifugation at 2000 rpm. At this point, any fat was removed from the top of the cells.

Buffer and dilute cell suspension with buffer were removed to cytocrit of 5-10%. The cells were kept at 37°C for 1 hour.

3. Glucose uptake

500 μl buffer was added with or without additives (insulin 10-10,000 μU/ml, peptides 0.1-10μM) to 10 ml plastic tubes.

500 μl aliquots of the cell suspension were added to the tubes.

After incubation for 30 minutes at 37°C in a shaking water bath (approximately 300 strokes/minute), 200 μl of buffer containing 3H - Deoxy Glucose (approx. 1200 cpm/μl) was added to each tube.

After 30 minutes incubation with 3H-DOG at 37°C, 200 μl aliquots were transferred to microcentrifuge tubes containing 200 μl Dinonyl phthalate. Cells were rapidly separated from the aqueous buffer by centrifugation at 10,000g for 30-60 sec. Cells separated in the top layer from the aqueous buffer by Dinonyl phthalate.

Cell associated radioactivity was counted in a liquid scintillation counter.

Inhibition of Glucose-Uptake by IRK-Derived Peptide

Glucose-uptake was measured in fresh adipocytes, incubated with or without insulin (10μU) as described above, in the absence (control) or the presence of 10μM of peptide K094D101 (derived from the αD region of IRK). The results are shown in Table III.

Table III: Glucose-Uptake: Mean DPM ± SEM of Quadruplicates

	-Insulin	+Insulin 10 μU/ml
Control	1,149 ± 122	1,803 ± 136
+K094D101	775 ± 72	1,210 ± 110
%K094D101 / Control	67%	67%

These results show that peptides from the αD region of IRK inhibit the uptake of glucose by adipocytes, in the presence or absence of insulin.

Example 6 - The Induction of Melanogenesis by a Peptide Derived from the αD Region of Jak 2

B16 melanoma cells (a mouse tumor cell line) were cultured in a 24-well plate, 10^5 cells/well, in the presence of various concentrations of K085D102, a Jak2-derived peptide from the αD region. After 5 days incubation in DMEM + 10% fetal calf serum under standard conditions, the plate was observed by eye for melanogenesis. Melanogenesis induction was visualized by an increase in the amount of the black pigment in the well. The results of this visualization test showed a dose response down to a concentration as low as 0.15μM of the Jak2 peptide of the αD region present in the well.

Equivalents

Those skilled in the art will be able to recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments

of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

CLAIMS

What is claimed is:

1. A peptide comprising a peptide derivative of the αD region of a protein kinase, wherein:
   a) said peptide has between about five and about thirty amino acids or amino acid analogs; and
   b) said peptide modulates activity of the protein kinase.

2. The peptide of Claim 1 wherein the peptide is cyclic.

3. The peptide of Claim 1 wherein the peptide is linear.

4. The peptide of Claim 3 wherein the N-terminus and the C-terminus of the peptide are unsubstituted.

5. The peptide of Claim 3 wherein at least one of the N-terminus or the C-terminus is substituted.

6. The peptide of Claim 5 wherein the N-terminus is amidated and the C-terminus is acylated.

7. The peptide of Claim 3 wherein the peptide derivative has an amino acid sequence corresponding to any subsequence of the amino acid sequence of said αD region of said protein kinase, with the proviso that any one amino acid in the sequence of the peptide derivative can vary, being any amino acid or analog thereof.

8. The peptide of Claim 3 wherein the protein kinase is member of a protein kinase family selected from the group of families consisting of G protein-

coupled receptor kinases, cyclin dependent kinases, Src family kinases, endothelial growth factor receptor kinases, fibroblast growth factor receptor kinases, Tyk/Jak kinases, insulin receptor kinases, TGFβ receptor kinases, activin receptor-like kinases, neurotrophin receptor kinases, I-kappa B kinases, discoidin domain receptor kinases, and integrin-linked kinase.

9. The peptide of Claim 8 wherein the protein kinase is a G protein-coupled kinase selected from the group consisting of bARK1, bARK2, GRK1, GRK4, GRK5 and GRK6.

10. The peptide of Claim 8 wherein the protein kinase is a cyclin dependent kinase selected from the group consisting of CDK2, CDK4 and CDK6.

11. The peptide of Claim 8 wherein the protein kinase is a Src family kinase selected from the group consisting of c-Src, c-Yes, Fyn, C-Fgr, Lyn, Hck, Lck, Csk and Matk.

12. The peptide of Claim 8 wherein the protein kinase is an endothelial growth factor receptor kinase selected from the group onsisting of Tie, Tek, PDGFR-b, PDGFR-a, Flt1, Flt4 and Flk1.

13. The peptide of Claim 8 wherein the protein kinase is a fibroblast growth factor receptor kinase selected from the group consisting of Flg, Bek, FGFR-3 and FGFR-4.

14. The peptide of Claim 8 wherein the protein kinase is a Tyk/Jak kinase selected from the group consisting of Jak1, Jak2, Jak3 and Tyk2.

15. The peptide of Claim 8 wherein the protein kinase is a discoidin domain receptor kinase selected from the group consisting of DDR1 and DDR2.

16. The peptide of Claim 8 wherein the protein kinase is a TGFβ receptor kinase selected from the group consisting of TGFbRII, ACTRIIA and ACTRIIB.

17. The peptide of Claim 8 wherein the protein kinase is an activin receptor-like kinase selected from the group consisting of ALK1, ALK2, ALK3, ALK4, ALK5 and ALK6.

18. The peptide of Claim 8 wherein the protein kinase is a neurotrophin receptor kinase selected from the group consisting of Trk, TrkB, and TrkC.

19. The peptide of Claim 8 wherein the protein kinase is ILK.

20. The peptide of Claim 8 wherein the protein kinase is IRK.

21. The peptide of Claim 8 wherein protein kinase is an I-kappa B kinase selected from the group consisting of IKK-1 and IKK-2.

22. The peptide of Claim 3 wherein the peptide derivative has an amino acid sequence corresponding to any subsequence of the amino acid sequence of said αD region.

23. The peptide of Claim 3 wherein the peptide has the sequence of Akt1/Raca K014D001; ALK1 K048D101; Braf K003D001 K003D101; c-Abl K061D101; c-Met K073D101; c-Raf K001D101 K001D001; c-Sea K074D101; c-Src K051D101 K051D001; CDK2 K049D101 K049D001; CDK4 K050D001 K050D101; CDK6 K089D101; Chk1 K088D102 K088D101; CK IIα K022D001 K022D101; Csk K058D101 K058D001; Fak K060D101; FGFR-3 K071D101 K071D001 K071D102 K071D901; Flk1 K068D102 K068D101 K068D001 K068D901; GSK3ß K018D003 K018D002 K018D101 K018D001; Hck K056D101; Iak1 K087D101; IKK-1 K090D101; IKK2 K091D101; ILK K107D101 K107D901; IRK K094D001

K094D101 K094D102 K094D103 K094D104; Jak1 K084D101 K084D102; Jak2 K085D102 K085D105; Jak3 K086D101 K086D102 K086D103; Lck K057D001 K057D101; Lyn K055D101; MARK1 K045D101; PDGFR-b K064D001 K064D101; PKCß K008D101 K008D001; Plk K035D001 K035D101 K035D102; Ret K080D101 K080D001; Ron K075D101; SNK K038D101; Syk K082D101; TGFβRII K093D101; TrkB K102D101 K102D106 K102D107 K102D108 K102D109; Zap70 K083D101 (SEQ ID NO: 95 to 170, respectively), as specified in Fig. 3.

24. A peptide having the sequence of Akt1/Raca K014D001; ALK1 K048D101; Braf K003D001 K003D101; c-Abl K061D101; c-Met K073D101; c-Raf K001D101 K001D001; c-Sea K074D101; c-Src K051D101 K051D001; CDK2 K049D101 K049D001; CDK4 K050D001 K050D101; CDK6 K089D101; Chk1 K088D102 K088D101; CK IIα K022D001 K022D101; Csk K058D101 K058D001; Fak K060D101; FGFR-3 K071D101 K071D001 K071D102 K071D901; Flk1 K068D102 K068D101 K068D001 K068D901; GSK3ß K018D003 K018D002 K018D101 K018D001; Hck K056D101; Iak1 K087D101; IKK-1 K090D101; IKK2 K091D101; ILK K107D101 K107D901; IRK K094D001 K094D101 K094D102 K094D103 K094D104; Jak1 K084D101 K084D102; Jak2 K085D102 K085D105; Jak3 K086D101 K086D102 K086D103; Lck K057D001 K057D101; Lyn K055D101; MARK1 K045D101; PDGFR-b K064D001 K064D101; PKCß K008D101 K008D001; Plk K035D001 K035D101 K035D102; Ret K080D101 K080D001; Ron K075D101; SNK K038D101; Syk K082D101; TGFβRII K093D101; TrkB K102D101 K102D106 K102D107 K102D108 K102D109; Zap70 K083D101 (SEQ ID NO: 95 to 170, respectively) as specified in Fig.3, with the proviso that any one amino acid residue in the peptide can vary, being any naturally occurring amino acid or analog thereof.

25. A peptide comprising a sequence of amino acids AA_1 through AA_{23} or a subsequence thereof comprising at least five amino acids, wherein:

AA_1 is selected from the group consisting of leucine, methionine, isoleucine and valine;

AA_2 is selected from the group consisting of aspartic acid, threonine, glutamic acid, serine and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of a glutamic acid or aspartic acid;

AA_3 is selected from the group consisting of leucine, isoleucine, methionine and valine;

AA_4 is selected from the group consisting of methionine, isoleucine, leucine and valine;

AA_5 is selected from the group consisting of asparagine and glutamine;

AA_6 is selected from the group consisting of glycine and alanine;

AA_7 is selected from the group consisting of glycine and alanine;

AA_8 is selected from the group consisting of aspartic acid, glutamic acid and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of a glutamic acid or aspartic acid;

AA_9 is selected from the group consisting of leucine, isoleucine, methionine and valine;

AA_{10} is selected from the group consisting of histidine, arginine and lysine;

AA_{11} is selected from the group consisting of tyrosine, phenylalanine and tryptophan;

AA_{12} is histidine;

AA_{13} is selected from the group consisting of leucine, isoleucine, methionine and valine;

AA_{14} is selected from the group consisting of serine, tyrosine, threonine, phenylalanine and tryptophan;

AA_{15} is selected from the group consisting of glutamine, asparagine and histidine;

AA_{16} is selected from the group consisting of histidine, valine, leucine, methionine and isoleucine;

AA_{17} is selected from the group consisting of glycine, aspartic acid, glutamic acid, alanine and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of a glutamic acid or aspartic acid;

AA_{18} is selected from the group consisting of valine, glutamic acid, asparagine, glutamine, isoleucine, leucine, methionine, aspartic acid and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of a glutamic acid or aspartic acid;

AA_{19} is selected from the group consisting of pheynylalanine, aspartic acid, proline, alanine, tryptophan, tyrosine, glutamic acid, glycine and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of a glutamic acid or aspartic acid;

AA_{20} is selected from the group consisting of asparagine, glycine, glutamine and alanine;

AA_{21} is selected from the group consisting of proline, phenylalanine, tryptophan and tyrosine;

AA_{22} is selected from the group consisting of glycine and alanine; and

AA_{23} is selected from the group consisting of phenylalanine, tryptophan and tyrosine.

26. The peptide of Claim 25 wherein the sequence AA_1 through AA_{23} or a subsequence thereof corresponds to a sequence of the αD region of a G protein-coupled receptor kinase selected from the group consisting of SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21 and SEQ ID NO: 22 or a subsequence thereof, with the proviso that any two amino acids in the sequence AA_1 through AA_{23} or the subsequence thereof can vary.

27. The peptide of Claim 25 wherein the sequence AA_1 through AA_{23} or a subsequence thereof corresponds to the sequence or a subsequence of the αD

region of a G protein- coupled receptor kinase selected from the group consisting of SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21 and SEQ ID NO: 22, with the proviso that any one amino acid in the sequence AA_1 through AA_{23} or the subsequence thereof can vary.

28. A peptide comprising a sequence of amino acids AA_1 through AA_{20} or a subsequence thereof comprising at least five amino acids, wherein:

AA_1 is selected from the group consisting of phenylalanine, tryptophan and tyrosine;

AA_2 is selected from the group consisting of glutamic acid, aspartic acid and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_3 is selected from the group consisting of phenylalanine, histidine, tryptophan and tyrosine;

AA_4 is selected from the group consisting of leucine, valine, isoleucine and methionine;

AA_5 is selected from the group consisting of histidine, aspartic acid, glutamic acid, and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_6 is selected from the group consisting of glutamine and asparagine;

AA_7 is selected from the group consisting of aspartic acid, glutamic acid and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_8 is selected from the group consisting of leucine, isolucine, methionine an valine;

AA_9 is selected from the group consisting of lysine, arginine, threonine and serine;

AA_{10} is selected from the group consisting of lysine, threonine, arginine and serine;

AA_{11} is selected from the group consisting of phenylalanine, tyrosine and tryptophan;

AA_{12} is selected from the group consisting of methionine, leucine, isoleucine and valine;

AA_{13} is selected from the group consisting of aspartic acid, glutamic acid and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_{14} is selected from the group consisting of alanine, lysine, arginine and glycine;

AA_{15} is selected from the group consisting of valine, serine, alanine, isoleucine, leucine, methionine and threonine;

AA_{16} is selected from the group consisting of alanine, proline and glycine;

AA_{17} is selected from the group consisting of leucine, proline, glutamic acid, isoleucine, methionine, valine, aspartic acid and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_{18} is selected from the group consisting of threonine, proline and serine;

AA_{19} is selected from the group consisting of glycine and alanine; and

AA_{20} is selected from the group consisting of isoleucine, leucine, valine and methionine.

29. The peptide of Claim 28 wherein the sequence AA_1 through AA_{20} or a subsequence thereof corresponds to a sequence of the αD region of a cyclin dependent kinase selected from the group consisting of SEQ ID NO: 35, SEQ ID NO: 36 and SEQ ID NO: 37 or a subsequence thereof, with the proviso that any two amino acids in the sequence AA_1 through AA_{20} or the subsequence thereof can vary.

30. The peptide of Claim 28 wherein the sequence AA_1 through AA_{20} or a subsequence thereof corresponds to a sequence of the αD region of a cyclin dependent kinase selected from the group consisting of SEQ ID NO: 35, SEQ ID NO: 36 and SEQ ID NO: 37 or a subsequence thereof, with the proviso that any one amino acid in the sequence AA_1 through AA_{20} or the subsequence thereof can vary.

31. A peptide comprising a sequence of amino acids AA_1 through AA_{21} or a subsequence thereof comprising at least five amino acids, wherein:

AA_1 is selected from the group consisting of threonine, methionine, serine, isoleucine, leucine and valine;

AA_2 is selected from the group consisting of glutamic acid, aspartic acid and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_3 is selected from the group consisting of phenylalanine, tyrosine, histidine and tryptophan;

AA_4 is selected from the group consisting of methionine, valine, isoleucine and leucine;

AA_5 is selected from the group consisting of serine, asparagine, cysteine, alanine, glutamic acid, threonine, glutamine, aspartic acid, glycine and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_6 is selected from the group consisting of lysine, histidine, asparagine, arginine and glutamine;

AA_7 is selected from the group consisting of glycine and alanine;

AA_8 is selected from the group consisting of serine, asparagine, threonine and glutamine;

AA_9 is selected from the group consisting of leucine, isoleucine, methionine and valine;

AA_{10} is selected from the group consisting of leucine, valine, isoleucine and methionine;

AA_{11} is selected from the group consisting of aspartic acid, asparagine, glutamic acid, glutamine and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_{12} is selected from the group consisting of phenylalanine, tyrosine and tryptophan;

AA_{13} is selected from the group consisting of leucine, isoleucine, methionine and valine;

AA_{14} is selected from the group consisting of lysine and arginine;

AA_{15} is selected from the group consisting of glycine, glutamic acid, aspartic acid, asparagine, serine, threonine, glutamine, alanine and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_{16} is selected from the group consisting of glutamic acid, glycine, proline, aspartic acid, arginine, lysine, alanine and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_{17} is selected from the group consisting of threonine, serine, aspartic acid, glutamic acid, glycine, alanine and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_{18} is selected from the group consisting of glycine, arginine, lysine and alanine;

AA_{19} is selected from the group consisting of lysine, arginine, glutamine, glycine, serine, isoleucine, alanine, asparagine, threonine, leucine, methionine and valine;

AA_{20} is selected from the group consisting of tyrosine, alanine, aspartic acid, lysine, valine, leucine, phenylalanine, tryptophan, glutamic acid, arginine, isoleucine, methionine, glycine and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid; and

AA_{21} is selected from the group consisting of leucine, valine, glutamine, isoleucine, methionine and asparagine.

32. The peptide of Claim 31 wherein the sequence AA_1 through AA_{21} or a subsequence thereof corresponds to the sequence of the αD region of a Src family kinase selected from the group consisting of SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45 and SEQ ID NO: 46 or a subsequence thereof, with the proviso that any two amino acids in the sequence AA_1 through AA_{21} or the subsequence thereof can vary.

33. The peptide of Claim 31 wherein the sequence AA_1 through AA_{21} or a subsequence thereof corresponds to the sequence of the αD region of a Src family kinase selected from the group consisting of SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45 and SEQ ID NO: 46 or a subsequence thereof, with the proviso that any one amino acid in the sequence AA_1 through AA_{21} or the subsequence thereof can vary.

34. A peptide comprising a sequence of amino acids AA_1 through AA_{39} or a subsequence thereof comprising at least five amino acids, wherein:

AA_1 is selected from the group consisting of isoleucine, threonine, valine, leucine, methionine and serine;

AA_2 is selected from the group consisting of glutamic acid, aspartic acid and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_3 is selected from the group consisting of tyrosine, phenylalanine and tryptophan;

AA_4 is selected from the group consisting of alanine, cysteine, serine, thronine and glycine;

AA_5 is selected from the group consisting of glycine, arginine, phenylalanine, lysine, tryptophan and tyrosine;

AA_6 is selected from the group consisting of tyrosine, histidine, phenylalanine and tryptophan;

AA_7 is selected from the group consisting of glycine and alanine;

AA_8 is selected from the group consisting of asparagine, aspartic acid, glutamine, glutamic acid and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_9 is selected from the group consisting of leucine, isoleucine, methionine and valine;

AA_{10} is selected from the group consisting of leucine, valine, serine, isoleucine, methionine and threonine;

AA_{11} is selected from the group consisting of aspartic acid, asparagine, threonine, glutamic acid, glutamine, serine and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_{12} is selected from the group consisting of phenylalanine, tyrosine and tryptophan;

AA_{13} is selected from the group consisting of leucine, isoleucine, methionine and valine;

AA_{14} is selected from the group consisting of arginine, histidine and lysine;

AA_{15} is selected from the group consisting of lysine, arginine, serine, alanine, glycine and threonine;

AA_{16} is selected from the group consisting of serine, asparagine, lysine, threonine, glutamine and arginine;

AA_{17} is selected from the group consisting of arginine and lysine;

AA_{18} is selected from the group consisting of valine, histidine, aspartic acid, asparagine, isoleucine, leucine, methionine, glutamic acid, glutamine

and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_{19} is selected from the group consisting of leucine, threonine, serine, alanine, glutamic acid, isoleucine, methionine, valine, aspartic acid, glycine and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_{20} is selected from the group consisting of glutamic acid, phenylalnine, aspartic acid, tryptophan, tyrosine and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_{21} is selected from the group consisting of threonine, leucine, phenylalanine, serine, valine, isoleucine, methionine, tryptophan and tyrosine;

AA_{22} is selected from the group consisting of aspartic acid, glutamine, serine, leucine, proline, glutamic acid, asparagine, threonine, isoleucine, methionine, valine and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_{23} is selected from the group consisting of proline, histidine, asparagine, cysteine, tyrosine, glutamine, phenylalanine, tryptophan, and serine;

AA_{24} is selected from the group consisting of alanine, histidine, lysine, arginine and glycine;

AA_{25} is selected from the group consisting of phenylalanine, serine, proline, aspartic acid, glutamic acid, tryptophan, tyrosine, threonine and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_{26} is selected from the group consisting of alanine, aspartic acid, glutamic acid, lysine, arginine, glycine and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_{27} is selected from the group consisting of arginine, isoleucine, lysine, alanine, serine, glycine, leucine, methionine, valine and threonine;

AA_{28} is selected from the group consisting of glutamic acid, alanine, arginine, proline, leucine, aspartic acid, lysine, isoleucine, methionine, valine, glycine and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_{29} is selected from the group consisting of histidine, asparagine, arginine, lysine, glutamic acid, glutamine, aspartic acid and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_{30} is selected from the group consisting of glycine, serine, proline, lysine, methionine, glutamine, phenylalanine, threonine, arginine, isoleucine, leucine, valine, asparagine, tryptophan, tyrosine and alanine;

AA_{31} is selected from the group consisting of threonine, proline, glutamic acid, arginine, serine, aspartic acid, lysine and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_{32} is selected from the group consisting of serine, alanine, aspartic acid, lysine, arginine, glycine, threonine, glutamic acid and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_{33} is selected from the group consisting of threonine, glutamic acid, isoleucine, lysine, phenylaline, serine, aspartic acid, leucine, methionine, valine, arginine, tryptophan, tyrosine and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_{34} is selected from the group consisting of leucine, phenylalanine, glutamic acid, arginine, aspartic acid, isoleucine, methionine, valine, tryptophan, tyrosine, lysine and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_{35} is selected from the group consisting of tyrosine, glycine, lysine, alanine, phenylalanine, tryptophan and arginine;

AA_{36} is selected from the group consisting of serine, leucine, methionine, valine, threonine, and isoleucine;

AA_{37} is selected from the group consisting of asparagine, glutamic acid, valine, glycine, glutamine, aspartic acid, isoleucine, leucine, methionine, alanine and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_{38} is selected from the group consisting of alanine, proline, glutamic acid, aspartic acid, glycine and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_{39} is selected from the group consisting of leucine, alanine, glycine, isoleuine, methionine and valine.

35. The peptide of Claim 34 of the sequence AA_1 through AA_{39} or a subsequence thereof corresponds to the sequence of the αD region of an endothelial growth factor receptor kinase selected from the group consisting of SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58 and SEQ ID NO: 59 or a subsequence thereof, with the proviso that any two amino acids in the sequence AA_1 through AA_{39} or the subsequence thereof can vary.

36. The peptide of Claim 34 wherein the sequence AA_1 through AA_{39} or a subsequence thereof corresponds to the sequence of the αD region of an endothelial growth factor receptor kinase selected from the group consisting of SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58 and SEQ ID NO: 59 or a subsequence thereof, with the proviso that any one amino acid in the sequence AA_1 through AA_{39} or the subsequence thereof can vary.

37. A peptide comprising a sequence of amino acids AA_1 through AA_{34} or a subsequence thereof comprising at least five amino acids, wherein:

AA_1 is selected from the group consisting of valine, isoleucine, leucine and methionine;

AA_2 is selected from the group consisting of glutamic acid, aspartic acid and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_3 is selected from the group consisting of tyrosine, cysteine, phenylalanine, tryptophan and serine;

AA_4 is selected from the group consisting of alanine and glycine;

AA_5 is selected from the group consisting of serine, alanine, threonine and glycine;

AA_6 is selected from the group consisting of lysine and arginine;

AA_7 is selected from the group consisting of glycine and alanine;

AA_8 is selected from the group consisting of asparagine and glutamine;

AA_9 is selected from the group consisting of leucine, isoleucine, methionine and valine;

AA_{10} is selected from the group consisting of arginine and lysine;

AA_{11} is selected from the group consisting of glutamic acid, aspartic acid and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_{12} is selected from the group consisting of tyrosine, phenylalanine and tryptophan;

AA_{13} is selected from the group consisting of leucine, isoleucine, methionine and valine;

AA_{14} is selected from the group consisting of glutamine, arginine, asparagine and lysine;

AA_{15} is selected from the group consisting of alanine and glycine;

AA_{16} is selected from the group consisting of arginine and lysine;

AA_{17} is selected from the group consisting of arginine and lysine;

AA_{18} is proline;

AA_{19} is proline;

AA_{20} is selected from the group consisting of glycine and alanine;

AA_{21} is selected from the group consisting of leucine, methionine, proline, isoleucine and valine;

AA_{22} is selected from the group consisting of glutamic acid, aspartic acid and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_{23} is selected from the group consisting of tyrosine, leucine, phenylalanine, tryptophan, isoleucine, methionine and valine;

AA_{24} is selected from the group consisting of cysteine, serine and threonine;

AA_{25} is selected from the group consisting of tyrosine, phenylalanine, proline and tryptophan;

AA_{26} is selected from the group consisting of asparagine, aspartic acid, glutamine, glutamic acid and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_{27} is selected from the group consisting of proline, isoleucine, threonine, glycine, leucine, methionine, valine, serine and alanine;

AA_{28} is selected from the group consisting of serine, asparagine, cysteine, proline, threonine and glutamine;

AA_{29} is selected from the group consisting of histidine, arginine and lysine;

AA_{30} is selected from the group consisting of asparagine, valine, proline, serine, glutamine, isoleucine, leucine, methionine and threonine;

AA_{31} is selected from the group consisting of proline, serine and threonine;

AA_{32} is selected from the group consisting of glutamic acid, glycine, aspartic acid, alanine and an aliphatic, substituted aliphatic, benzyl,

substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_{33} is selected from the group consisting of glutamine, proline and asparagine; and

AA_{34} is selected from the group consisting of leucine, methionine, isoleucine and valine.

38. The peptide of Claim 37 wherein the sequence AA_1 through AA_{34} or a subsequence thereof corresponds to the sequence of the αD region of a fibroblast growth factor receptor kinase selected from the group consisting of SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53 and SEQ ID NO: 54 or a subsequence thereof, with the proviso that any two amino acids in the sequence AA_1 through AA_{34} or the subsequence thereof can vary.

39. The peptide of Claim 37 wherein the sequence AA_1 through AA_{34} or a subsequence thereof corresponds to the sequence of the αD region of a fibroblast growth factor receptor kinase selected from the group consisting of SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53 and SEQ ID NO: 54 or a subsequence thereof, with the proviso that any one amino acid in the sequence AA_1 through AA_{34} or the subsequence thereof can vary.

40. A peptide comprising a sequence of amino acids AA_1 through AA_{20} or a subsequence thereof comprising at least five amino acids, wherein:

AA_1 is selected from the group consisting of methionine, isoleucine, leucine and valine;

AA_2 is selected from the group consisting of glutamic acid, aspartic acid and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_3 is selected from the group consisting of phenylalanine, tyrosine, and tryptophan;

AA_4 is selected from the group consisting of leucine, isoleucine, methionine and valine;

AA_5 is proline;

AA_6 is selected from the group consisting of serine, tyrosine, threonine, phenylalanine, tryptophan, leucine and isoleucine;

AA_7 is selected from the group consisting of glycine and alanine;

AA_8 is selected from the group consisting of serine, cysteine and threonine;

AA_9 is selected from the group consisting of leucine, isoleucine, methionine and valine;

AA_{10} is selected from the group consisting of lysine and arginine;

AA_{11} is selected from the group consisting of glutamic acid, aspartic acid and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_{12} is selected from the group consisting of tyrosine, phenylalanine and tryptophan;

AA_{13} is selected from the group consisting of leucine, isoleucine, methionine and valine;

AA_{14} is selected from the group consisting of proline, glutamine, and asparagine;

AA_{15} is selected from the group consisting of lysine and arginine;

AA_{16} is selected from the group consisting of asparagine, histidine and glutamine;

AA_{17} is selected from the group consisting of lysine, arginine, serine and threonine;

AA_{18} is selected from the group consisting of asparagine, glutamic acid, alanine, glutamine, aspartic acid, glycine, isoleucine, leucine and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_{19} is selected from the group consisting of lysine and arginine; and

AA_{20} is selected from the group consisting of isoleucine, leucine, methionine and valine.

41. The peptide of Claim 38 wherein the sequence AA_1 through AA_{20} or a subsequence thereof corresponds to the sequence of the αD region of a Tyk/Jak kinase selected from the group consisting of SEQ ID NO: 73, SEQ ID NO: 74, SEQ ID NO: 75 and SEQ ID NO: 76 or a subsequence thereof, with the proviso that any two amino acids in the sequence AA_1 through AA_{20} or the subsequence thereof can vary.

42. The peptide of Claim 38 wherein the sequence AA_1 through AA_{20} or a subsequence thereof corresponds to the sequence of the αD region of a Tyk/Jak kinase selected from the group consisting of SEQ ID NO: 73, SEQ ID NO: 74, SEQ ID NO: 75 and SEQ ID NO: 76 or a subsequence thereof, with the proviso that any one amino acid in the sequence AA_1 through AA_{20} or the subsequence thereof can vary.

43. A peptide comprising a sequence of amino acids AA_1 through AA_{31} or a subsequence thereof comprising at least five amino acids, wherein:

AA_1 is selected from the group consisting of methionine, isoleucine, leucine and valine;

AA_2 is selected from the group consisting of glutamic acid, aspartic acid and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_3 is selected from the group consisting of leucine, isoleucine, methionine and valine;

AA_4 is selected from the group consisting of methionine, isoleucine, leucine and valine;

AA_5 is selected from the group consisting of alanine and glycine;

AA_6 is histidine;

AA_7 is selected from the group consisting of glycine and alanine;

AA_8 is selected from the group consisting of aspartic acid, glutamic acid and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_9 is selected from the group consisting of leucine, isoleucine, methionine and valine;

AA_{10} is selected from the group consisting of lysine and arginine;

AA_{11} is selected from the group consisting of serine and threonine;

AA_{12} is selected from the group consisting of tyrosine, phenylalanine and tryptophan;

AA_{13} is selected from the group consisting of leucine, isoleucine, methionine and valine;

AA_{14} is selected from the group consisting of arginine and lysine;

AA_{15} is selected from the group consisting of serine and threonine;

AA_{16} is selected from the group consisting of leucine, isoleucine, methionine and valine;

AA_{17} is selected from the group consisting of arginine and lysine;

AA_{18} is proline;

AA_{19} is selected from the group consisting of glutamic acid, aspartic acid and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_{20} is selected from the group consisting of alanine and glycine;

AA_{21} is selected from the group consisting of glutamic acid, aspartic acid and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_{22} is selected from the group consisting of asparagine and glutamine;

AA_{23} is selected from the group consisting of asparagine and glutamine;

AA_{24} is proline;

AA_{25} is selected from the group consisting of glycine and alanine;

AA_{26} is selected from the group consisting of arginine and lysine;

AA_{27} is proline;

AA_{28} is proline;

AA_{29} is proline;

AA_{30} is selected from the group consisting of threonine and serine; and

AA_{31} is selected from the group consisting of leucine, isoleucine, methionine and valine.

44. The peptide of Claim 43 wherein the sequence AA_1 through AA_{31} or a subsequence thereof corresponds to the sequence of the αD region of SEQ ID NO: 82 or a subsequence thereof, with the proviso that any two amino acids in the sequence AA_1 through AA_{31} or the subsequence thereof can vary.

45. The peptide of Claim 43 wherein the sequence AA_1 through AA_{31} or a subsequence thereof corresponds to the sequence of the αD region of SEQ ID NO: 82 or a subsequence thereof, with the proviso that any one amino acid in the sequence AA_1 through AA_{31} or the subsequence thereof can vary.

46. A peptide comprising a sequence of amino acids AA_1 through AA_{18} or a subsequence thereof comprising at least five amino acids, wherein:

AA_1 is selected from the group consisting of threonine and serine;

AA_2 is selected from the group consisting of alanine and glycine;

AA_3 is selected from the group consisting of phenylalanine, tryptophan and tyrosine;

AA_4 is histidine;

AA_5 is selected from the group consisting of alanine, glutamic acid, aspartic acid, glycine and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_6 is selected from the group consisting of lysine and arginine;

AA_7 is selected from the group consisting of glycine and alanine;

AA_8 is selected from the group consisting of asparagine, serine, glutamine and threonine;

AA_9 is selected from the group consisting of leucine, isoleucine, methionine and valine;

AA_{10} is selected from the group consisting of glutamine, serine and threonine;

AA_{11} is selected from the group consisting of glutamic acid, aspartic acid and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_{12} is selected from the group consisting of tyrosine, phenylalanine and tryptophan;

AA_{13} is selected from the group consisting of leucine, isoleucine, methionine and valine;

AA_{14} is selected from the group consisting of threonine, lysine, serine and arginine;

AA_{15} is selected from the group consisting of arginine, alanine, glycine and lysine;

AA_{16} is selected from the group consisting of histidine, asparagine and glutamine;

AA_{17} is selected from the group consisting of valine, isoleucine, leucine and methionine; and

AA_{18} is selected from the group consisting of isoleucine, valine, leucine and methionine.

47. The peptide of Claim 46 wherein the sequence AA_1 through AA_{18} or a subsequence thereof corresponds to the sequence of the αD region of a TGFβ receptor kinase selected from the group consisting of SEQ ID NO: 83, SEQ ID NO: 84 and SEQ ID NO: 85 or a subsequence thereof, with the proviso that any two amino acids in the sequence AA_1 through AA_{18} or the subsequence thereof can vary.

48. The peptide of Claim 44 wherein the sequence AA_1 through AA_{18} or a subsequence thereof corresponds to the sequence of the αD region of a TGFβ rceptor kinase selected from the group consisting of SEQ ID NO: 83, SEQ ID NO: 84 and SEQ ID NO: 85 or a subsequence thereof, with the proviso that any one amino acid in the sequence AA_1 through AA_{18} or the subsequence thereof can vary.

49. A peptide comprising a sequence of amino acids AA_1 through AA_{18} or a subsequence thereof comprising at least five amino acids, wherein:

AA_1 is selected from the group consisting of threonine and serine;

AA_2 is selected from the group consisting of histidine, aspartic acid, glutamic acid and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_3 is selected from the group consisting of tyrosine, phenylalanine and tryptophan;

AA_4 is histidine;

AA_5 is selected from the group consisting of glutamic acid, aspartic acid and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_6 is selected from the group consisting of histidine, methionine, asparagine, isoleucine, leucine, valine and glutamine;

AA_7 is selected from the group consisting of glycine and alanine;

AA_8 is selected from the group consisting of serine and threonine;

AA_9 is selected from the group consisting of leucine, isoleucine, methionine and valine;

AA_{10} is selected from the group consisting of tyrosine, phenylalanine and tryptophan;

AA_{11} is selected from the group consisting of aspartic acid, glutamic acid and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_{12} is selected from the group consisting of phenylalanine, tyrosine and tryptophan;

AA_{13} is selected from the group consisting of leucine, isoleucine, methionine and valine;

AA_{14} is selected from the group consisting of glutamine, lysine, asparagine and arginine;

AA_{15} is selected from the group consisting of arginine, leucine, cysteine, serine, lysine, isoleucine, methionine, valine and threonine;

AA_{16} is selected from the group consisting of glutamine, threonine, alanine, tyrosine, asparagine, serine, phenylalanine, tryptophan and glycine;

AA_{17} is selected from the group consisting of threonine and serine; and

AA_{18} is selected from the group consisting of leucine, valine, isoleucine and methionine.

50. The peptide of Claim 47 wherein the sequence AA_1 through AA_{18} or a subsequence thereof corresponds to the sequence of the αD region of an activin receptor-like kinase selected from the group consisting of SEQ ID NO: 86, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 89 and SEQ ID NO: 90 or a subsequence thereof, with the proviso that any two amino acids in the sequence AA_1 through AA_{18} or the subsequence thereof can vary.

51. The peptide of Claim 47 wherein the sequence AA_1 through AA_{18} or a subsequence thereof corresponds to the sequence of the αD region of an activin receptor-like kinase selected from the group consisting of SEQ ID NO: 86, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 89 and SEQ ID NO: 90 or a subsequence thereof, with the proviso that any one amino acid in the sequence AA_1 through AA_{18} or the subsequence thereof can vary.

52. A peptide comprising a sequence of amino acids AA_1 through AA_{34} or a subsequence thereof comprising at least five amino acids, wherein:

AA_1 is selected from the group consisting of phenylalanine, tryptophan and tyrosine;

AA_2 is selected from the group consisting of glutamic acid, aspartic acid and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_3 is selected from the group consisting of tyrosine, phenylalanine and tryptophan;

AA_4 is selected from the group consisting of methionine, isoleucine, leucine and valine;

AA_5 is selected from the group consisting of arginine and lysine;

AA_6 is histidine;

AA_7 is selected from the group consisting of glycine and alanine;

AA_8 is selected from the group consisting of aspartic acid, glutamic acid and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_9 is selected from the group consisting of leucine, isoleucine, methionine and valine;

AA_{10} is selected from the group consisting of asparagine and glutamine;

AA_{11} is selected from the group consisting of arginine and lysine;

AA_{12} is selected from the group consisting of phenylalanine, tryptophan and tyrosine;

AA_{13} is selected from the group consisting of leucine, isoleucine, methionine and valine;

AA_{14} is selected from the group consisting of arginine and lysine;

AA_{15} is selected from the group consisting of serine, alanine, threonine and glycine;

AA_{16} is histidine;

AA_{17} is selected from the group consisting of glycine and alanine;

AA_{18} is proline;

AA_{19} is selected from the group consisting of aspartic acid, glutamic acid and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_{20} is selected from the group consisting of alanine and glycine;

AA_{21} is selected from the group consisting of lysine, valine, methionine, arginine, isoleucine and leucine;

AA_{22} is selected from the group consisting of leucine, isoleucine, methionine and valine;

AA_{23} is selected from the group consisting of leucine, methionine, isoleucine and valine;

AA_{24} is selected from the group consisting of alanine, valine, isoleucine, leucine, methionine and glycine;

AA_{25} is selected from the group consisting of glycine, glutamic acid, aspartic acid, alanine and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_{26} is selected from the group consisting of glycine and alanine;

AA_{27} is selected from the group consisting of glutamic acid, asparagine, glutamine, aspartic acid and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_{28} is selected from the group consisting of aspartic acid, proline, glutamic acid and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_{29} is selected from the group consisting of valine, proline, arginine, isoleucine, leucine, methionine and lysine;

AA_{30} is selected from the group consisting of alanine, threonine, glutamine, serine, asparagine and glycine;

AA_{31} is selected from the group consisting of proline, glutamic acid, alanine, aspartic acid, glycine and an aliphatic, substituted aliphatic, benzyl,

substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_{32} is selected from the group consisting of proline, glycine and alanine;

AA_{33} is selected from the group consisting of leucine, glutamic acid, isoleucine, methionine, valine, aspartic acid and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid; and

AA_{34} is selected from the group consisting of leucine, isoleucine, methionine and valine.

53. The peptide of Claim 52 wherein the sequence AA_1 through AA_{34} or a subsequence thereof corresponds to the sequence of the αD region of a neurotrophic receptor kinase selected from the group consisting of SEQ ID NO: 68, SEQ ID NO: 69 and SEQ ID NO: 70 or a subsequence thereof, with the proviso that any two amino acids in the sequence AA_1 through AA_{34} or the subsequence thereof can vary.

54. The peptide of Claim 52 wherein the sequence AA_1 through AA_{18} or a subsequence thereof corresponds to the sequence of the αD region of a neurotrophic receptor kinase selected from the group consisting of SEQ ID NO: 68, SEQ ID NO: 69 and SEQ ID NO: 70 or a subsequence thereof, with the proviso that any one amino acid in the sequence AA_1 through AA_{31} or the subsequence thereof can vary.

55. A peptide comprising a sequence of amino acids AA_1 through AA_{21} or a subsequence thereof comprising at least five amino acids, wherein:

AA_1 is selected from the group consisting of threonine and serine;

AA_2 is histidine

AA_3 is selected from the group consisting of tryptophan, phenylalanine and tyrosine;

AA_4 is selected from the group consisting of methionine, isoleucine, leucine and methionine;

AA_5 is proline;

AA_6 is selected from the group consisting of tyrosine, phenylalanine and tryptophan;

AA_7 is selected from the group consisting of glycine and alanine;

AA_8 is selected from the group consisting of serine and threonine;

AA_9 is selected from the group consisting of leucine, isoleucine, methionine and valine;

AA_{10} is selected from the group consisting of tyrosine, phenylalanine and tryptophan;

AA_{11} is selected from the group consisting of asparagine and glutamine;

AA_{12} is selected from the group consisting of valine, isoleucine, leucine and methionine;

AA_{13} is selected from the group consisting of leucine, isoleucine, methionine and valine;

AA_{14} is histidine;

AA_{15} is selected from the group consisting of glutamic acid, aspartic acid and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_{16} is selected from the group consisting of glycine and alanine;

AA_{17} is selected from the group consisting of threonine and serine;

AA_{18} is selected from the group consisting of asparagine and glutamine;

AA_{19} is selected from the group consisting of phenylalanine, tryptophan and tyrosine;

AA_{20} is selected from the group consisting of valine, isoleucine, leucine and methionine; and

AA_{21} is selected from the group consisting of valine, isoleucine, leucine and methionine.

56. The peptide of Claim 55 wherein the sequence AA_1 through AA_{21} or a subsequence thereof corresponds to the sequence of the αD region of SEQ ID NO: 93 or a subsequence thereof, with the proviso that any two amino acids in the sequence AA_1 through AA_{21} or the subsequence thereof can vary.

57. The peptide of Claim 55 wherein the sequence AA_1 through AA_{21} or a subsequence thereof corresponds to the sequence of the αD region of SEQ ID NO: 93 or a subsequence thereof, with the proviso that any one amino acid in the sequence AA_1 through AA_{21} or the subsequence thereof can vary.

58. A peptide comprising a sequence of amino acids AA_1 through AA_{22} or a subsequence thereof comprising at least five amino acids, wherein:

AA_1 is selected from the group consisting of methionine, isoleucine, leucine and valine;

AA_2 is selected from the group consisting of glutamic acid, aspartic acid and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_3 is selected from the group consisting of tyrosine, phenylalanine and tryptophan;

AA_4 is selected from the group consisting of cysteine and serine;

AA_5 is selected from the group consisting of serine, glutamine, threonine and asparagine;

AA_6 is selected from the group consisting of glycine and alanine;

AA_7 is selected from the group consisting of glycine and alanine;

AA_8 is selected from the group consisting of aspartic acid, glutamic acid and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_9 is selected from the group consisting of leucine, isoleucine, methionine and valine;

AA_{10} is selected from the group consisting of arginine and lysine;

AA_{11} is selected from the group consisting of lysine and asparagine;

AA_{12} is selected from the group consisting of leucine, tyrosine, isoleucine, methionine, valine, phenylalanine and tryptophan;

AA_{13} is selected from the group consisting of leucine, isoleucine, methionine and valine;

AA_{14} is selected from the group consisting of asparagine and glutamine;

AA_{15} is selected from the group consisting of lysine, glutamine, arginine and asparagine;

AA_{16} is selected from the group consisting of proline, phenylalanine, tryptophan and tyrosine;

AA_{17} is selected from the group consisting of glutamic acid, aspartic acid and an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic ester of glutamic acid or aspartic acid;

AA_{18} is selected from the group consisting of asparagine and glutamine;

AA_{19} is selected from the group consisting of cysteine and serine;

AA_{20} is selected from the group consisting of cysteine and serine;

AA_{21} is selected from the group consisting of glycine and alanine; and

AA_{22} is selected from the group consisting of leucine, isoleucine, methionine and valine.

59. The peptide of Claim 58 wherein the sequence AA_1 through AA_{22} or a subsequence thereof corresponds to the sequence of the αD region of an I-kappa B kinase selected from the group consisting of SEQ ID NO: 79 and SEQ ID NO: 80 or a subsequence thereof, with the proviso that any two amino acids in the sequence AA_1 through AA_{22} or the subsequence thereof can vary.

60. The peptide of Claim 58 wherein the sequence AA_1 through AA_{22} or a subsequence thereof corresponds to the sequence of the αD region of an I-

kappa B kinase selected from the group consisting of SEQ ID NO: 79 and SEQ ID NO: 80 or a subsequence thereof, with the proviso that any one amino acid in the sequence AA_1 through AA_{22} or the subsequence thereof can vary.

61. A method of identifying a peptide which modulates the activity of a protein kinase comprising the steps of:

a) providing a peptide, referred to as a "test peptide", comprising a peptide derivative of the αD region of said protein kinase and having from about five to about thirty amino acids or analogs thereof;

b) incubating the test peptide with cells having one or more cellular activities controlled by a protein kinase under conditions suitable for assessing activity of the protein kinase;

c) assessing activity of the protein kinase, wherein greater or lesser activity compared with the cells grown without incubation of the test peptide indicates that the peptide modulates activity of the protein kinase.

62. The method of Claim 61, wherein the activity of the protein kinase is assessed by measuring the rate of survival or proliferation of said cells in tissue culture.

63. A method of modulating the activity of a protein kinase in a subject, comprising administering a therapeutically effective amount of a peptide comprising a peptide derivative of the αD region of a protein kinase, wherein:

a) said peptide has between about five and about thirty amino acids or amino acid analogs; and

b) said peptide modulates activity of the protein kinase.

64. A method of detecting a ligand that binds to the αD region of a protein kinase comprising:

a) providing a peptide derivative of the αD region of said protein kinase, said peptide derivative having at least five amino acids or analogs thereof;

b) incubating said peptide derivative with a sample, to be tested for the presence of said ligand, for a time sufficient for said ligand to bind to said peptide derivative; and

c) detecting any said ligand-said peptide derivative binding pair that has been formed in step b), wherein the presence of said ligand-said peptide derivative binding pair establishes the existence of said ligand in said sample.

65. The method of Claim 64 further comprising:

d) separating said ligand from said peptide derivative; and

e) determining the structure of said ligand, thereby identifying said ligand.

66. An antibody that immunologically binds to the αD region of a protein kinase.

67. A method of producing antibodies that bind to the αD region of a protein kinase comprising:

a) providing a peptide derivative of the αD region of said protein kinase, said peptide derivative having at least five amino acids; and

b) producing antibodies to said peptide derivatives.

Figure 1A

No.	Kinase-Subclass	Family	Sub	Protein	αD sequence
1	Serine/Threonine	RAF		c-Raf	TQWCEGSSLYKHLHVQETKF
2	Serine/Threonine	RAF		Araf	TQWCEGSSLYHHLHVADTRF
3	Serine/Threonine	RAF		Braf	TQWCEGSSLYHHLHIIETKF
4	Serine/Threonine	CAPK		cAPKa	MEYVPGGEMFSHLRRIGRF
4	Serine/Threonine	CAPK		cAPKb	MEYVPGGEMFSHLRRIGRF
5	Serine/Threonine	CAPK		cAPKg	MEYVPGGEMFSRLQRVGRF
6	Serine/Threonine	PKC		PKCa	MEYVNGGDLMYHIQQVGKF
7	Serine/Threonine	PKC		PKCb	MEYVNGGDLMYHIQQVGRF
8	Serine/Threonine	PKC		PKCg	MEYVTGGDLMYHIQQLGKF
9	Serine/Threonine	PKC		PKCd	MEFLNGGDLMFHIQDKGRF
10	Serine/Threonine	PKC		PKCe	MEYVNGGDLMFQIQRSRKF
11	Serine/Threonine	PKC		PKCet	MEFVNGGDLMFHIQKSRRF
12	Serine/Threonine	PKC		PKCth	MEYLNGGDLMYHIQSCHKF

Figure 1B

13	Serine/Threonine	Akt/PKB		Akt1/Raca	MEYANGGELFFHLSRERVF
13	Serine/Threonine	Akt/PKB		Akt2/Racb	MEYANGGELFFHLSRERVF
14	Serine/Threonine	GSK3		GSK3a	LEYVPETVYRVARHFTKAK LII
15	Serine/Threonine	GSK3		GSK3b	LDYVPETVYRVARHYSRAK QTL
16	Serine/Threonine	CK II		CK IIa	FEHVNNTDFKQLYQTL
17	Serine/Threonine	CK II		CK IIa'	FEYINNTDFKQLYQIL
18	Serine/Threonine	bARK1,2		bARK1	LDLMNGGDLHYHLSQHGV F
18	Serine/Threonine	bARK1,2		bARK2	LDLMNGGDLHYHLSQHGV F
19	Serine/Threonine	GRK1		GRK1	MTIMNGGDIRYHIYNVDED NPGF
20	Serine/Threonine	GRK4		GRK4	LTIMNGGDLKFHIYNLGNPG F
21	Serine/Threonine	GRK5		GRK5	LTIMNGGDLKFHIYNMGNP GF
22	Serine/Threonine	GRK6		GRK6	LTLMNGGDLKFHIYHMGQA GF

Figure 1C

23	Serine/Threonine	CaMK		CaMK I	MQLVSGGELFDRIVEKGGY
24	Serine/Threonine	CaMK		CaMK IIa	FDLVTGGELFEDIVAREYY
24	Serine/Threonine	CaMK		CaMK IIb	FDLVTGGELFEDIVAREYY
24	Serine/Threonine	CaMK		CaMK IIg	FDLVTGGELFEDIVAREYY
24	Serine/Threonine	CaMK		CaMK IId	FDLVTGGELFEDIVAREYY
25	Serine/Threonine	POLO		Plk	LELCRRRSLLELHKRRKAL
26	Serine/Threonine	POLO		Plx1	LELCRRRSLLELHKRRKAV
27	Serine/Threonine	POLO		polo	LELCKKRSMMELHKRRKSI
28	Serine/Threonine	POLO		SNK	LEYCSRRSMAHILKARKVL
29	Serine/Threonine	POLO		CDC5	LEICPNGSLMELLKRRKVL
30	Serine/Threonine	POLO		Sak	LEMCHNGEMNRYLKNRVK PF
31	Serine/Threonine	POLO		Prk	LELCSRKSLAHIWKARHTL

Figure 1D

31	Serine/Threonine	POLO		Fnk	LELCSRKSLAHIWKARHTL
32	Serine/Threonine	POLO		Plo1	LELCEHKSLMELLRKRKQL
33	Serine/Threonine	MARK/p78		MARK1	MEYASGGEVFDYLVAHGRM
33	Serine/Threonine	MARK/p78		MARK2	MEYASGGEVFDYLVAHGRM
34	Serine/Threonine	MARK/p78		P78	MEYASGGKVFDYLVAHGRM
35	Serine/Threonine	CDK		CDK2	FEFLHQDLKKFMDASALTGI
36	Serine/Threonine	CDK		CDK4	FEHVDQDLRTYLDKAPPPGL
37	Serine/Threonine	CDK		CDK6	FEHVDQDLTTYLDKVPEPGV
38	Tyrosine	SRC		c-Src	TEYMSKGSLLDFLKGETGKYL
39	Tyrosine	SRC		c-Yes	TEFMSKGSLLDFLKEGDGKYL
40	Tyrosine	SRC		Fyn	TEYMNKGSLLDFLKDGEGRAL
41	Tyrosine	SRC		c-Fgr	TEFMCHGSLLDFLKNPEGQDL

Figure 1E

42	Tyrosine	LYN/HCK		Lyn	TEYMAKGSLLDFLKSDEGGKV
43	Tyrosine	LYN/HCK		Hck	TEFMAKGSLLDFLKSDEGSKQ
44	Tyrosine	LCK		Lck	TEYMENGSLVDFLKTPSGIKL
45	Tyrosine	CSK		Csk	TEYMAKGSLVDYLRSRGRSVL
46	Tyrosine	CSK		Matk	MEHVSKGNLVNFLRTRGRALV
47	Tyrosine	FAK		Fak	MELCTLGELRSFLQVRKYSL
48	Tyrosine	ABL		c-Abl	TEFMTYGNLLDYLRECNRQEV
49	Tyrosine	ENDOTHELIAL	Tie/Tek	Tie	IEYAPYGNLLDFLRKSRVLETDPAFAREHGTASTL
50	Tyrosine	ENDOTHELIAL	Tie/Tek	Tek	IEYAPHGNLLDFLRKSRVLETDPAFAIANSTASTL
51	Tyrosine	ENDOTHELIAL	FGFR	Flg	VEYASKGNLREYLQARRPPGLEYCYNPSHNPEEQL
52	Tyrosine	ENDOTHELIAL	FGFR	Bek	VEYASKGNLREYLRARRPPGMEYSYDINRVPEEQM
53	Tyrosine	ENDOTHELIAL	FGFR	FGFR-3	VEYAAKGNLREFLRARRPPGLDYSFDTCKPPEEQL

Figure 1F

54	Tyrosine	ENDOTHELIAL	FGFR	FGFR-4	VECAAKGNLREFLRARRPPGPDLSPDGPRSSEGPL
55	Tyrosine	ENDOTHELIAL	PDGFR	PDGFR-a	TEYCFYGDLVNYLHKNRDSFLSHHPEKPKKELDIFGLNPA
56	Tyrosine	ENDOTHELIAL	PDGFR	PDGFR-b	TEYCRYGDLVDYLHRNKHTFLQHHSDKRRPPSAELYSNAL
57	Tyrosine	ENDOTHELIAL	Flt/Flk	Flt1	VEYCKYGNLSNYLKSKRDLFFLNKDAALHMEPKKEKMEPG
58	Tyrosine	ENDOTHELIAL	Flt/Flk	Flt4	VEFCKYGNLSNFLRAKRDAFSPCAEKSPEQRGRFRAMVEL
59	Tyrosine	ENDOTHELIAL	Flt/Flk	Flk1	VEFSKFGNLSTYLRGKRNEFVPYKSKGARFRQGKDYVGEL
60	Tyrosine	HGFR		c-Met	LPYMKHGDLRNFIRNETHNP
61	Tyrosine	HGFR		c-Sea	LPYMRHGDLRHFIRAQERSP
62	Tyrosine	HGFR		Ron	LPYMCHGDLLQFIRSPQRNP
63	Tyrosine	EGFR		EGFR	TQLMPFGCLLDYVREHKDNI
64	Tyrosine	EGFR		ErbB2	TQLMPYGCLLDHVRENRGRL
65	Tyrosine	EGFR		ErbB3	TQYLPLGSLLDHVRQHRGAL

Figure 1G

66	Tyrosine	EGFR		ErbB4	TQLMPHGCLLEYVHEHKDN I
67	Tyrosine	RET		Ret	VEYAKYGSLRGFLRESRKV GPGYLGSGGSRNSSSLDHPD ERAL
68	Tyrosine	TRK-NGFR		Trk - NGFR	FEYMRHGDLNRFLRSHGPD AKLLAGGEDVAPGPL
69	Tyrosine	TRK-NGFR		TrkB	FEYMKHGDLNKFLRAHGPD AVLMAEGNPPTEL
70	Tyrosine	TRK-NGFR		TrkC	FEYMKHGDLNKFLRAHGPD AMILVDGQPRQAKGEL
71	Tyrosine	SYK/ZAP70		Syk	MEMAELGPLNKYLQQNRH V
72	Tyrosine	SYK/ZAP70		Zap70	MEMAGGGPLHKFLVGKRE EI
73	Tyrosine	TYK/JAK		Jak1	MEFLPSGSLKEYLPKNKNKI
74	Tyrosine	TYK/JAK		Jak2	MEYLPYGSLRDYLQKHKER I
75	Tyrosine	TYK/JAK		Jak3	MEYLPSGCLRDFLQRHRAR L
76	Tyrosine	TYK/JAK		Tyk2	MEYVPLGSLRDYLPRHSI
77	Serine/Threonine	IAK		Iak1	LEYAPLGTVYRELQKLSKF

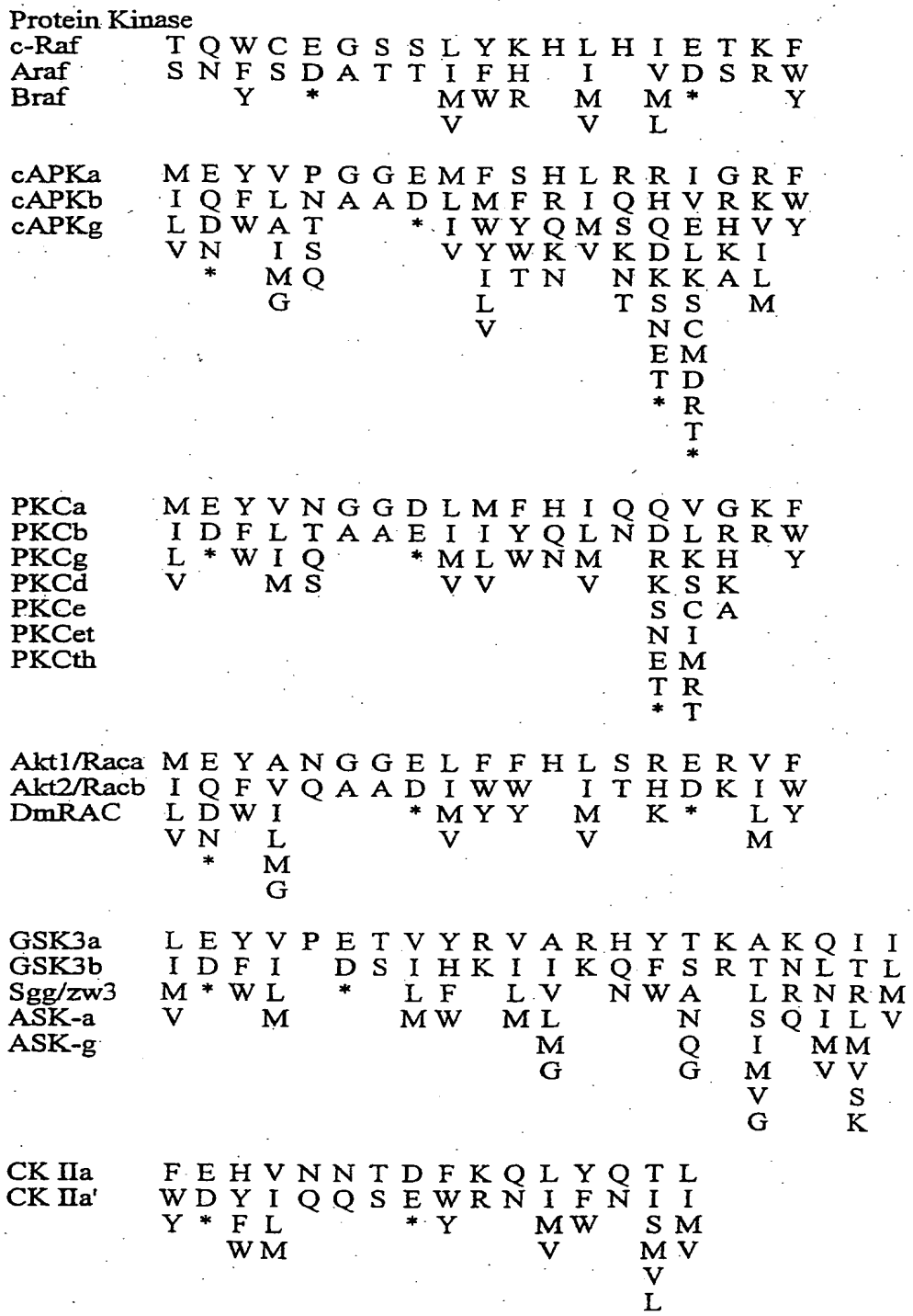
Figure 1H

78	Serine/Threonine	CHK		Chk1	LEYCSGGELFDRIEPDIGM
79	Serine/Threonine	IKK		IKK-1	MEYCSGGDLRKLLNKPENCCGL
80	Serine/Threonine	IKK		IKK-2	MEYCQGGDLRKYLNQFENCCGL
81	Serine/Threonine	DAPK		DAPK	LELVAGGELFDFLAEKESL
82	Tyrosine	IRK		IRK	MELMAHGDLKSYLRSLRPEAENNPGRPPPTL
83	Serine/Threonine	Activin/TGFbR	TGFbR	TGFbRII	TAFHAKGNLQEYLTRHVI
84	Serine/Threonine	Activin/TGFbR	ACTR	ACTRIIA	TAFHEKGSLSDFLKANVV
85	Serine/Threonine	Activin/TGFbR	ACTR	ACTRIIB	TAFHDKGSLTDYLKGNII
86	Serine/Threonine	Activin/TGFbR	ALK	ALK1	THYHEHGSLYDFLQRQTL
87	Serine/Threonine	Activin/TGFbR	ALK	ALK2	THYHEMGSLYDYLQLTTL
88	Serine/Threonine	Activin/TGFbR	ALK	ALK3	TDYHENGSLYDFLKCATL
89	Serine/Threonine	Activin/TGFbR	ALK	ALK4	SDYHEHGSLFDYLNRYTV

Figure 1I

89	Serine/Threonine	Activin/TGFbR	ALK	ALK5	SDYHEHGSLFDYLNRYTV
90	Serine/Threonine	Activin/TGFbR	ALK	ALK6	TDYHENGSLYDYLKSTTL
91	Tyrosine	DDR		DDR1	TDYMENGDLNQFLSAHQL
92	Tyrosine	DDR		DDR2	TEYMENGDLNQFLSRHEP
93	Serine/Threonine	ILK		ILK	THWMPYGSLYNVLHEGTNFVV
94	Tyrosine	MAPK		JNK	MELMDANLCQVIQMEL

Figure 2A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c-Raf
Araf
Braf
cAPKa
cAPKb
cAPKg
PKCa
PKCb
PKCg
PKCd
PKCe
PKCet
PKCth
Akt1/Raca
Akt2/Racb
DmRAC
GSK3a
GSK3b
Sgg/zw3
ASK-a
ASK-g
CK IIa
CK IIa'

Figure 2B

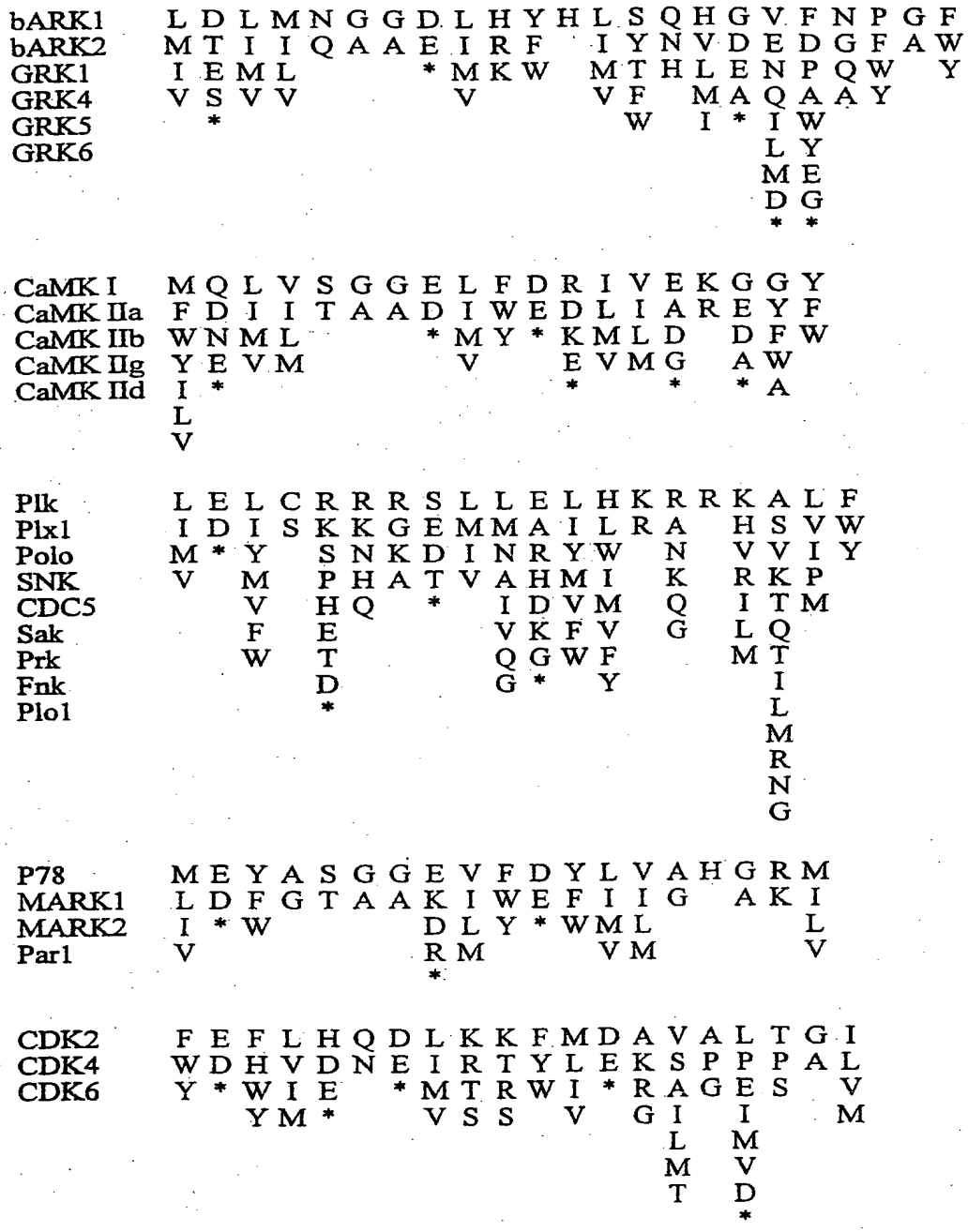


Figure 2C

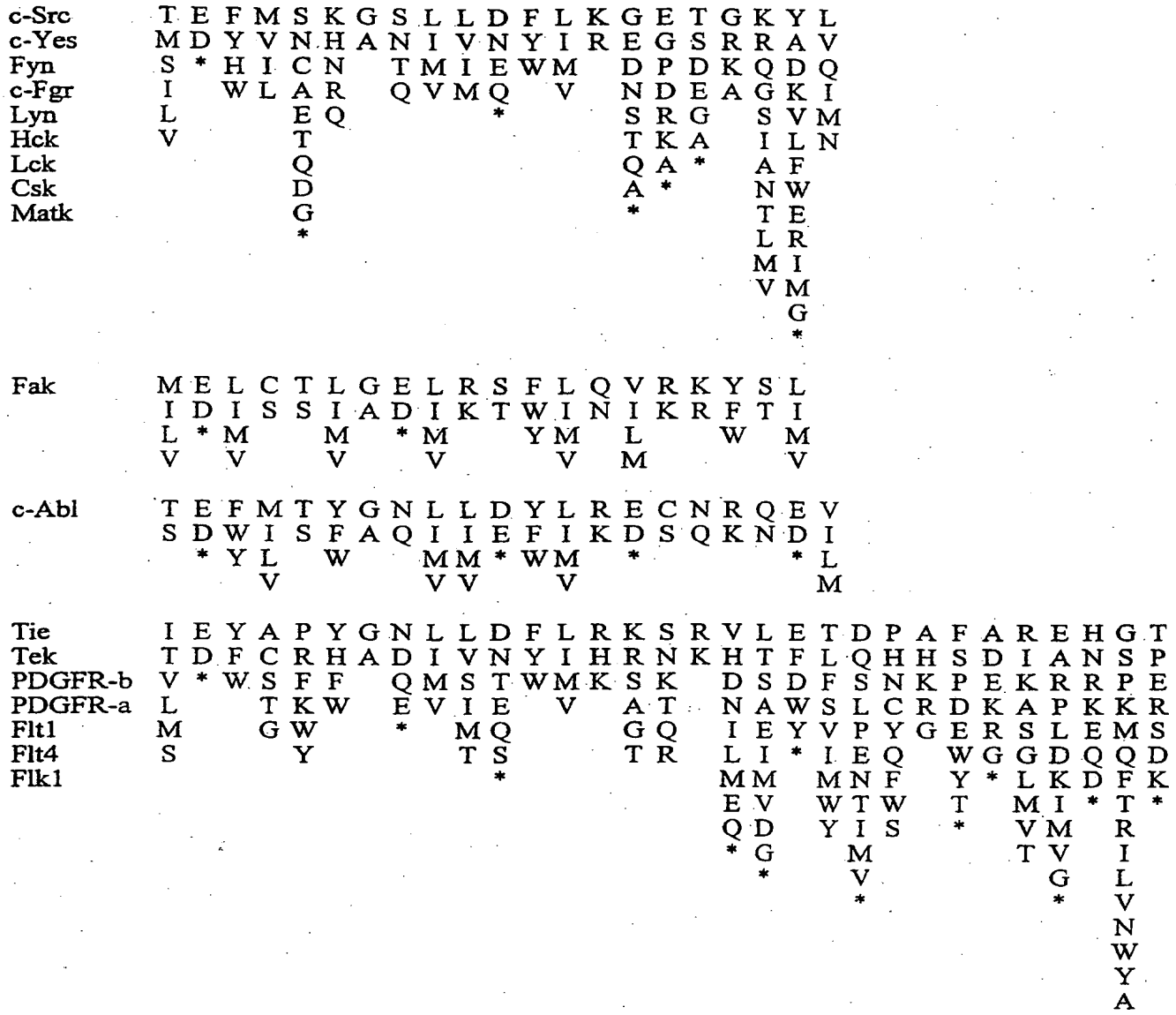
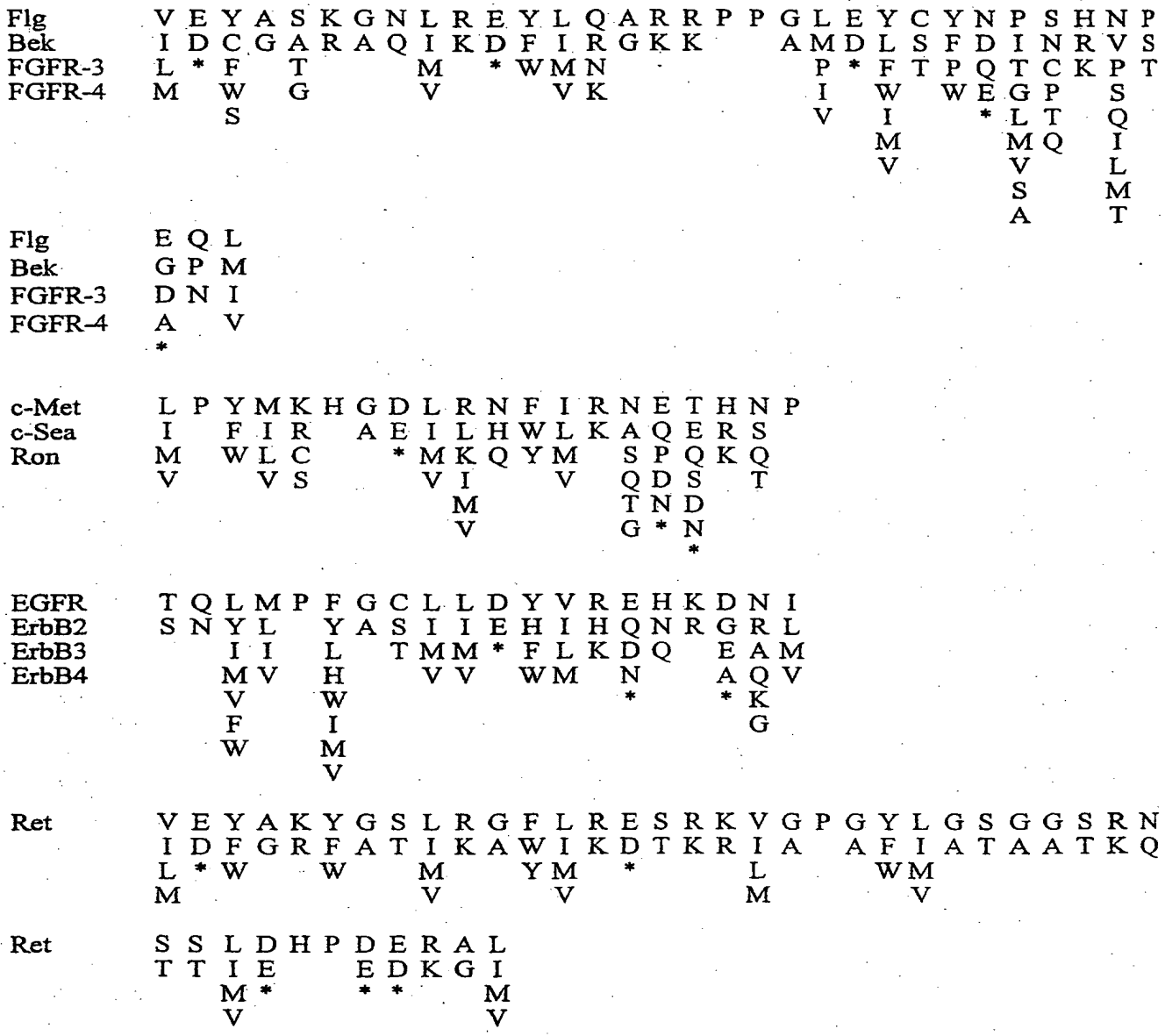


Figure 2D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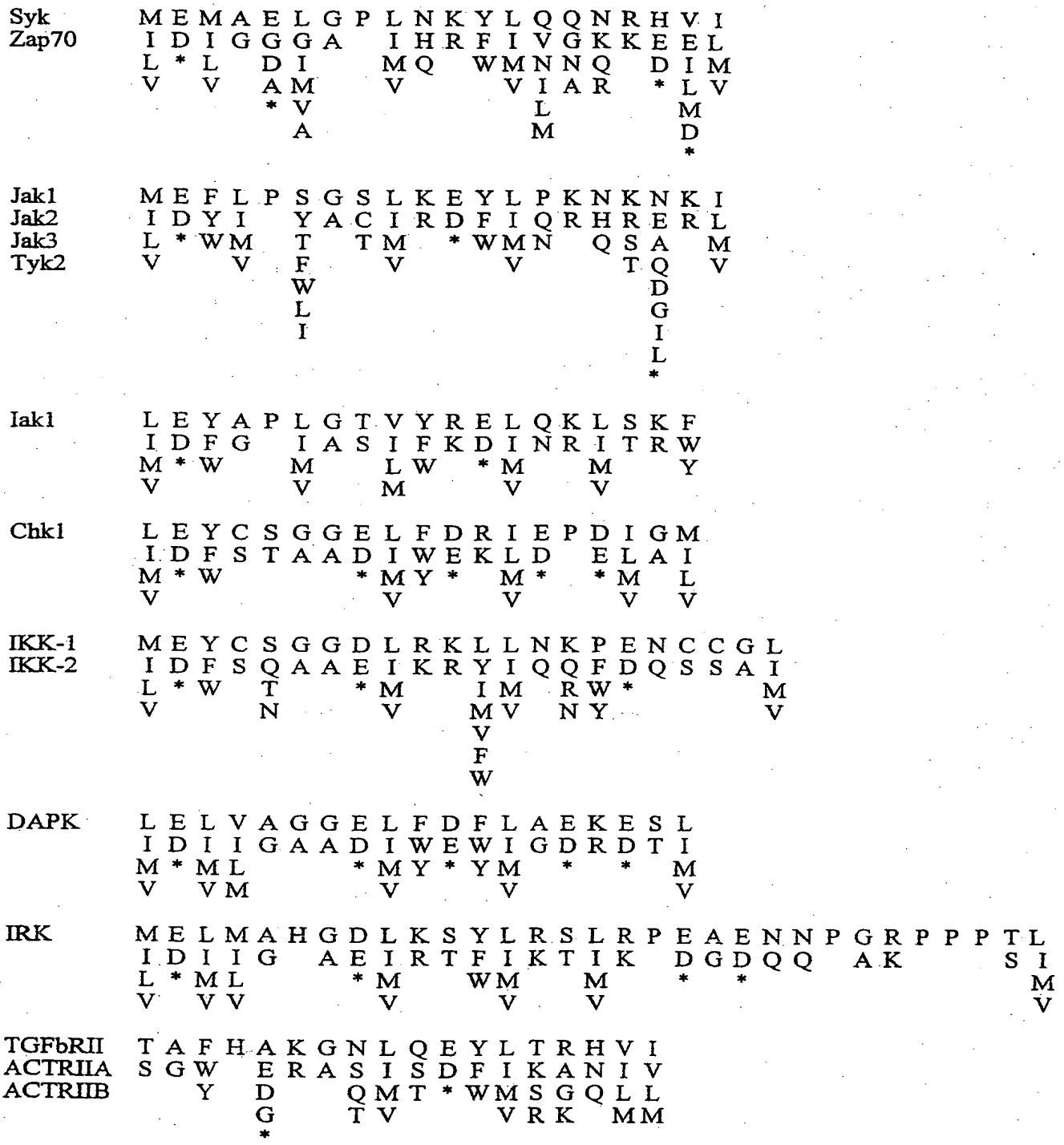
c-Met
c-Sea
Ron
EGFR
ErbB2
ErbB3
ErbB4
Ret
Ret

Figure 2E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Jak1
Jak2
Jak3
Tyk2
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Chk1
IKK-1
IKK-2
DAPK
IRK
TGFbRII
ACTRIIA
ACTRIIB

Figure 2F

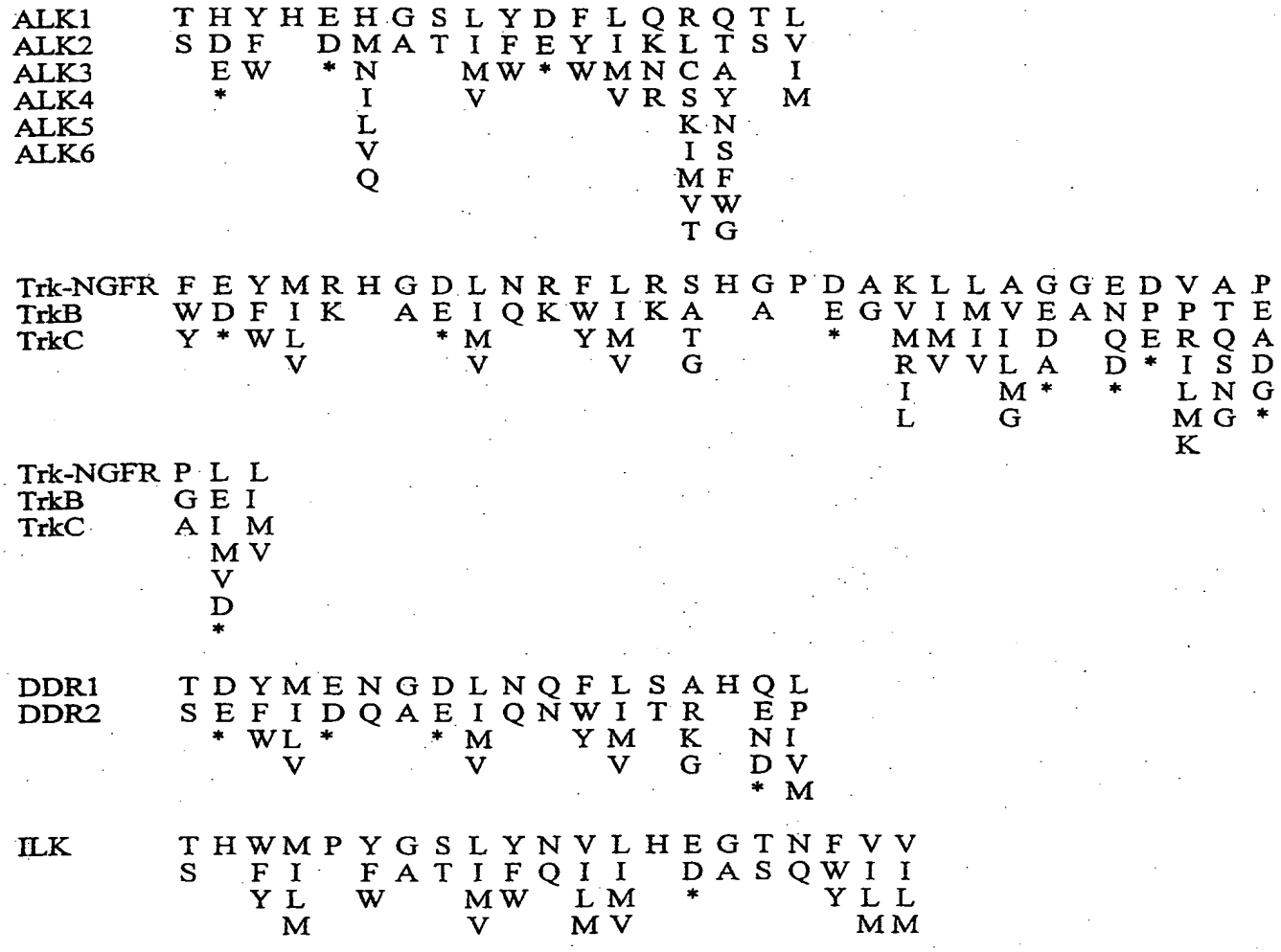

Figure 3A

Peptide	N-terminal	C-terminal
Akt1/Raca		
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ALK1		
96 K048D101	Myristyl - G T H Y H E H G S L Y D F L Q R Q T L	- NH2
Braf		
97 K003D001	Acetyl - K K K K K K G G S S L Y H H L H I I E T K F	- NH2
98 K003D101	Myristyl - G T Q W S E G S S L Y H H L H I I E T K F	- NH2
c-Abl		
99 K061D101	Myristyl - G T E F M T Y G N L L D Y L R E C N R Q E V	- NH2
c-Met		
100 K073D101	Myristyl - G L P Y M K H G D L R N F I R N E T H N P	- NH2
c-Raf		
101 K001D101	Myristyl - G T Q W S E G S S L Y K H L H V Q E T K F	- NH2
102 K001D001	Acetyl - S S L Y K H L H V Q E! T K F	- NH2
c-Sea		
103 K074D101	Myristyl - G L P Y M R H G D L R H F I R A Q E R S P	- NH2
c-Src		
104 K051D101	Myristyl - G T E Y M S K G S L L D F L K G E T G K Y L	- NH2
105 K051D001	Acetyl - G S L L D! L K G E! T G K F L	- NH2
CDK2		
106 K049D101	Myristyl - G F E F L H Q D L K K F M D A S A L T G I	- NH2
107 K049D001	Acetyl - D! L K K F M D! A S A L T G M	- NH2
CDK4		
108 K050D001	Acetyl - D! L R T Y L D! K A P P P G L	- NH2
109 K050D101	Myristyl - G F E H V D Q D L R T Y L D K A P P P G L	- NH2
CDK6		
110 K089D101	Myristyl - G F E H V D Q D L T T Y L D K V P E P G V	- NH2
Chk1		
111 K088D102	Myristyl - G E Y S S G G E L F D R I E P D I G M	- NH2
112 K088D101	Myristyl - G E Y A S G G E L F D R I E P D I G M	- NH2
CK IIa		
113 K022D001	Acetyl - K K K K K G G N N T D F K Q L Y Q T L	- NH2
114 K022D101	Myristyl - G F E H V N N T D F K Q L Y Q T L	- NH2

Figure 3B

Csk																															
115	K058D101	Myristyl -	G	T	E	Y	M	A	K	G	S	L	V	D	Y	L	R	S	R	G	R	S	V	L						- NH2
116	K058D001	Acetyl -	G	S	L	V	D!	L	R	S	R	G	R	S	V	L														- NH2
Fak																															
117	K060D101	Myristyl -	G	M	E	L	S	T	L	G	E	L	R	S	F	L	Q	V	R	K	Y	S	L							- NH2
FGFR-3																															
118	K071D101	Myristyl -	G	G	N	L	R	E	F	L	R	A	R	R	P	P	G	L	E											- NH2
119	K071D001	Acetyl -	G	N	L	R	E!	F	L	R	A	R	R	P	P	G	L	E!												- NH2
120	K071D102	Myristyl -	G	V	E	Y	A	A	K	G	N	L	R	E	F	L	R	A	R	R	P	P	G	L	E					- NH2
121	K071D901	Stearyl -	G	S	F	D	T	S	K	P	P	E	E	Q	L															- NH2
Flk1																															
122	K068D101	Myristyl -	G	V	E	F	S	K	F	G	N	L	S	N	F	L	R	A	K	R	N	L	F	V	P					- NH2
123	K068D101	Myristyl -	G	G	N	L	S	N	F	L	R	A	K	R	N	L	F	V	P											- NH2
124	K068D001	Acetyl -	G	N	L	S	N	F	L	R	A	K	R	N	L	F	V	P												- NH2
125	K068D901	Stearyl -	G	R	F	R	Q	G	K	D	Y	V	G	E	L															- NH2
GSK3b																															
126	K018D003	Acetyl -	K	K	K	K	K	K	G	G	G	V	A	R	H	Y	S	R	A	K	Q	T	L	P						- NH2
127	K018D002	Acetyl -	V	A	R	H	Y	S	R	A	K	Q	T	L	P															- NH2
128	K018D101	Myristyl -	G	D	Y	V	P	E	T	V	Y	R	V	A	R	H	Y	S	R	A	K	Q	T	L						- NH2
129	K018D001	Acetyl -	R	V	A	R	H	Y	S	R	A	K	Q	T																	- NH2
Hck																															
130	K056D101	Myristyl -	G	T	E	F	M	A	K	G	S	L	L	D	F	L	K	S	D	E	G	S	K	Q						- NH2
Jak1																															
131	K087D101	Myristyl -	G	L	E	Y	A	P	L	G	T	V	Y	R	E	L	Q	K	L	S	K	F								- NH2
IKK-1																															
132	K090D101	Myristyl -	G	M	E	Y	S	S	G	G	D	L	R	K	L	L	N	K	P	E	N	S	S	G	L					- NH2
IKK-2																															
133	K091D101	Myristyl -	G	M	E	Y	S	Q	G	G	D	L	R	K	Y	L	N	Q	F	E	N	S	S	G	L					- NH2
ILK																															
134	K107D101	Myristyl -	G	T	H	W	M	P	Y	G	S	L	Y	N	V	L	H	E	G	T	N	F	V	V						- NH2
135	K107D901	Stearyl -	G	Y	N	V	L	H	E	G	T	N	F	V	V															- NH2

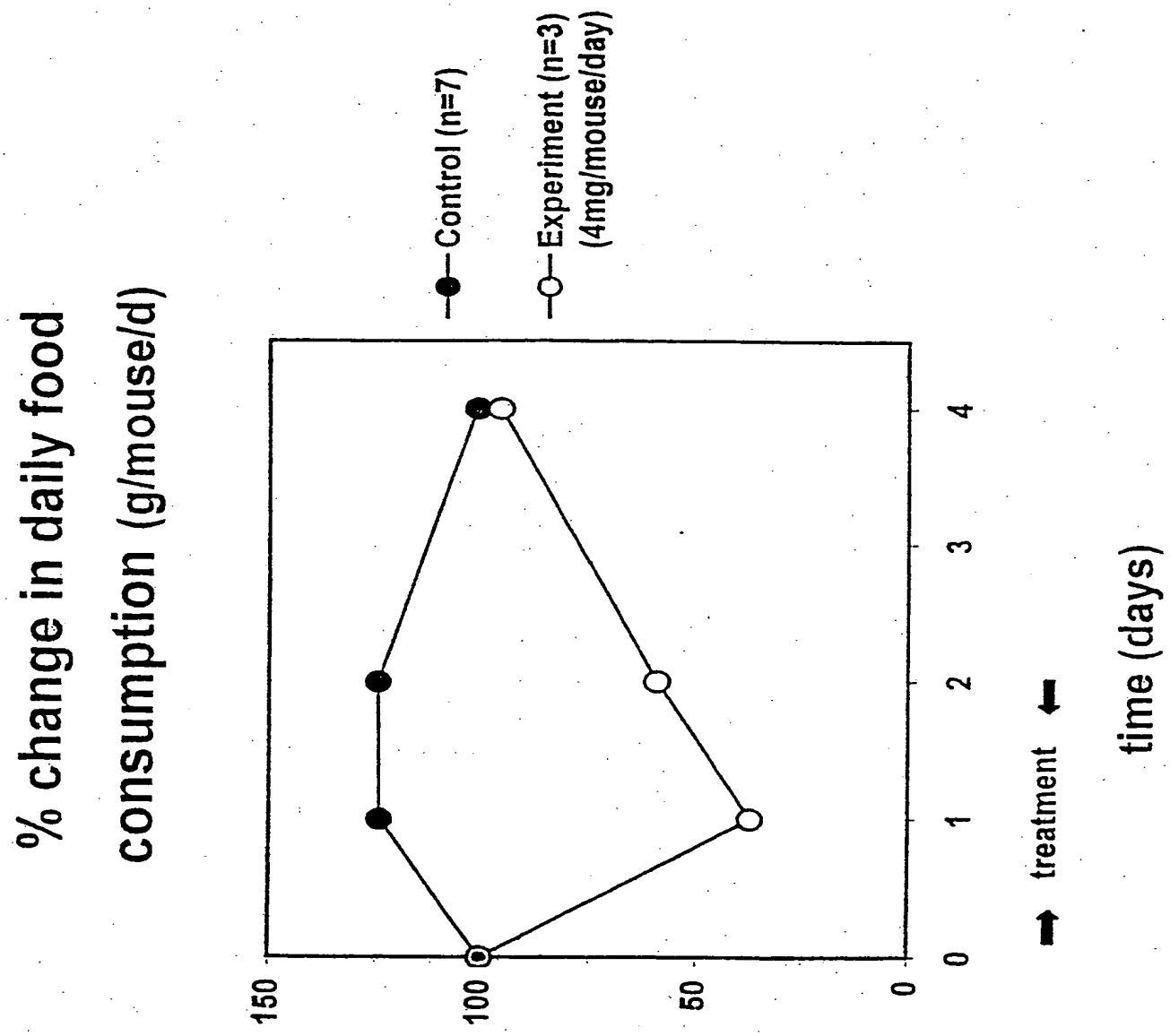
Figure 3C

	IRK		
136	K094D101	Myristyl - G M E L M A H G D L K S Y L R S L R P	- NH2
137	K094D001	Acetyl - A Q N N P G R P P P T L	- NH2
138	K094D102	Myristyl - G L K S Y L R S L R P E A	- NH2
139	K094D103	Myristyl - G A E N N P G R P P P T L	- NH2
140	K094D104	Myristyl - G L R P E A E N N P G R P P P T L	- NH2
	Jak1		
141	K084D101	Myristyl - G M E F L P S G S L K E Y L P K N K N K I	- NH2
142	K084D102	Myristyl - G L K E Y L P K N K N K I	- NH2
	Jak2		
143	K085D102	Myristyl - G L R D Y L Q K H K E R I	- NH2
144	K085D105	Stearyl - G L R D Y L Q K H K E	- NH2
	Jak3		
145	K086D101	Myristyl - G M E Y L P S G S L R D F L Q R H R A L	- NH2
146	K086D102	Myristyl - G M E Y L P S G S L R D F L Q R H R A R L	- NH2
147	K086D103	Myristyl - G L R D F L Q R H R A R L	- NH2
	Lck		
148	K057D001	Acetyl - G S L V D! L K T P S G I K L	- NH2
149	K057D101	Myristyl - G T E Y M E N G S L V D F L K T P S G I K L	- NH2
	Lyn		
150	K055D101	Myristyl - G T E Y M A K G S L L D F L K S D E G G K V	- NH2
	MARK1		
151	K045D101	Myristyl - G M E Y A S G G E V F D Y L V A H G R M	- NH2
	PDGFR-b		
152	K064D001	Acetyl - G D! L V D! Y L H R N K H T F L	- NH2
153	K064D101	Myristyl - G T E Y S R Y G D L V D Y L H R N K H T F L	- NH2
	PKCb		
154	K008D101	Myristyl - G M E Y V N G G D L M Y H I Q Q V G R F	- NH2
155	K008D001	Acetyl - K K K K K K G G D L M Y H I Q Q V G R F	- NH2
	Plk		
156	K035D001	Acetyl - R S L L E! L H K R R K A	- NH2
157	K035D101	Myristyl - G R S L L E! L H K R R K A	- NH2

Figure 3D

158	K035D102 Ret	Myristyl -	G	L	E	L	S	R	R	R	S	L	L	E	L	H	K	R	R	K	A	L					- NH2
159	K080D101	Myristyl -	G	V	E	Y	A	K	Y	G	S	L	R	G	F	L	R	E	S	R	K	V	G	P			- NH2
160	K080D001 Ron	Acetyl -	G	S	L	R	G	F	L	R	E!	S	R	K	V	G	P										- NH2
161	K075D101 SNK	Myristyl -	G	L	P	Y	M	C	H	G	D	L	L	Q	F	I	R	S	P	Q	R	N	P				- NH2
162	K038D101 Syk	Myristyl -	G	L	E	Y	S	S	R	R	S	M	A	H	I	L	K	A	R	K	V	L					- NH2
163	K082D101 TGFbRII	Myristyl -	G	M	E	M	A	E	L	G	P	L	N	K	Y	L	Q	Q	N	R	H	V					- NH2
164	K093D101 TrkB	Myristyl -	G	T	A	F	H	A	K	G	N	L	Q	E	Y	L	T	R	H	V	I						- NH2
165	K102D101	Myristyl -	G	F	E	Y	M	K	H	G	D	L	N	K	F	L	R	A	H	G	P	D	A	V	L	M	A - NH2
166	K102D106	Myristyl -	G	L	R	A	H	G	P	D	A	V	L	M	A												- NH2
167	K102D107	Myristyl -	G	L	R	A	H	G	P	D	A	V	L														- NH2
168	K102D108	Myristyl -	G	L	N	F	K	L	R	A	H	G	P	D	A												- NH2
169	K102D109 Zap70	Myristyl -	G	F	K	L	R	A	H	G	P	D	A	V	L												- NH2
170	K083D101	Myristyl -	G	M	E	M	A	G	G	G	P	L	H	K	F	L	V	G	K	R	E	E	I				- NH2

K:\RWAGNER\CMCC\679\FIGURES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Control (n=7)
Experiment (n=3) (4mg/mouse/day)
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100
50
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0
1
2
3
4
treatment
time (days)

Figure 4

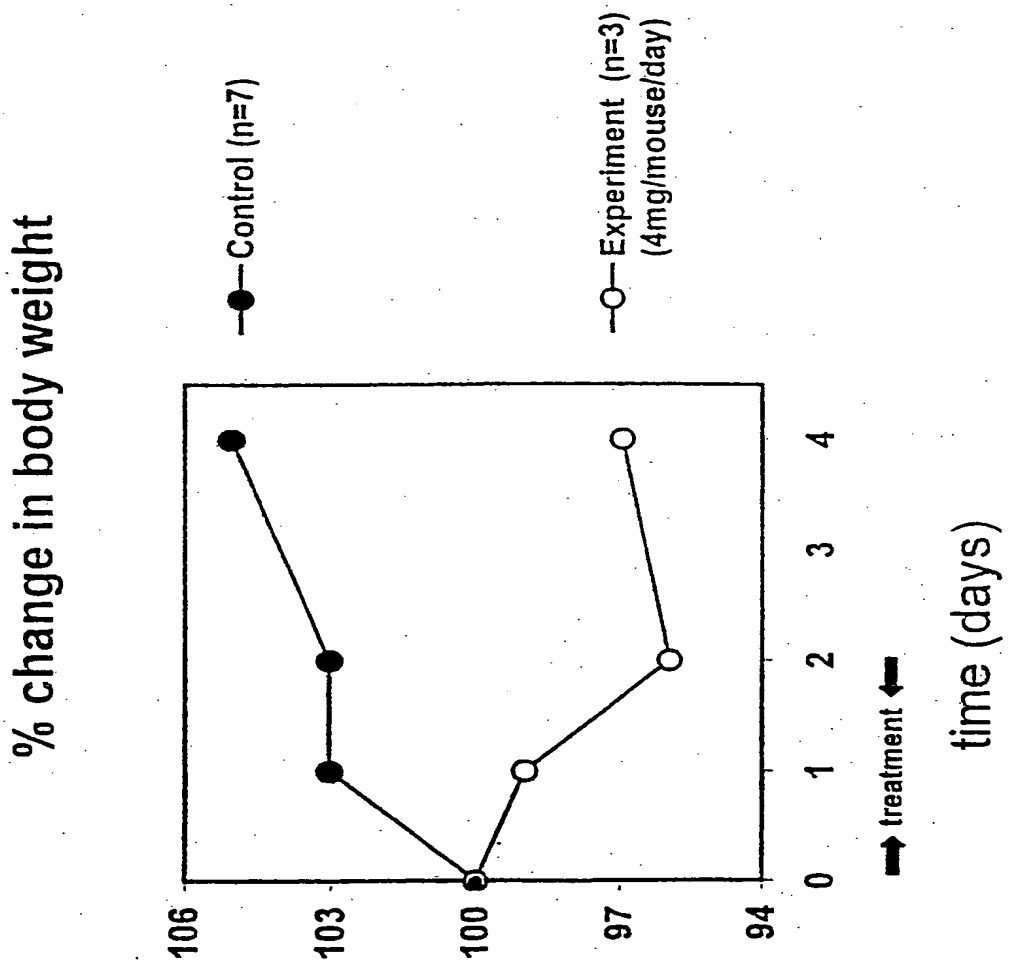

Figure 5

MODULATION OF TH1/TH2 DIFFERENTIATION BY A JAK-DERIVED PEPTIDE

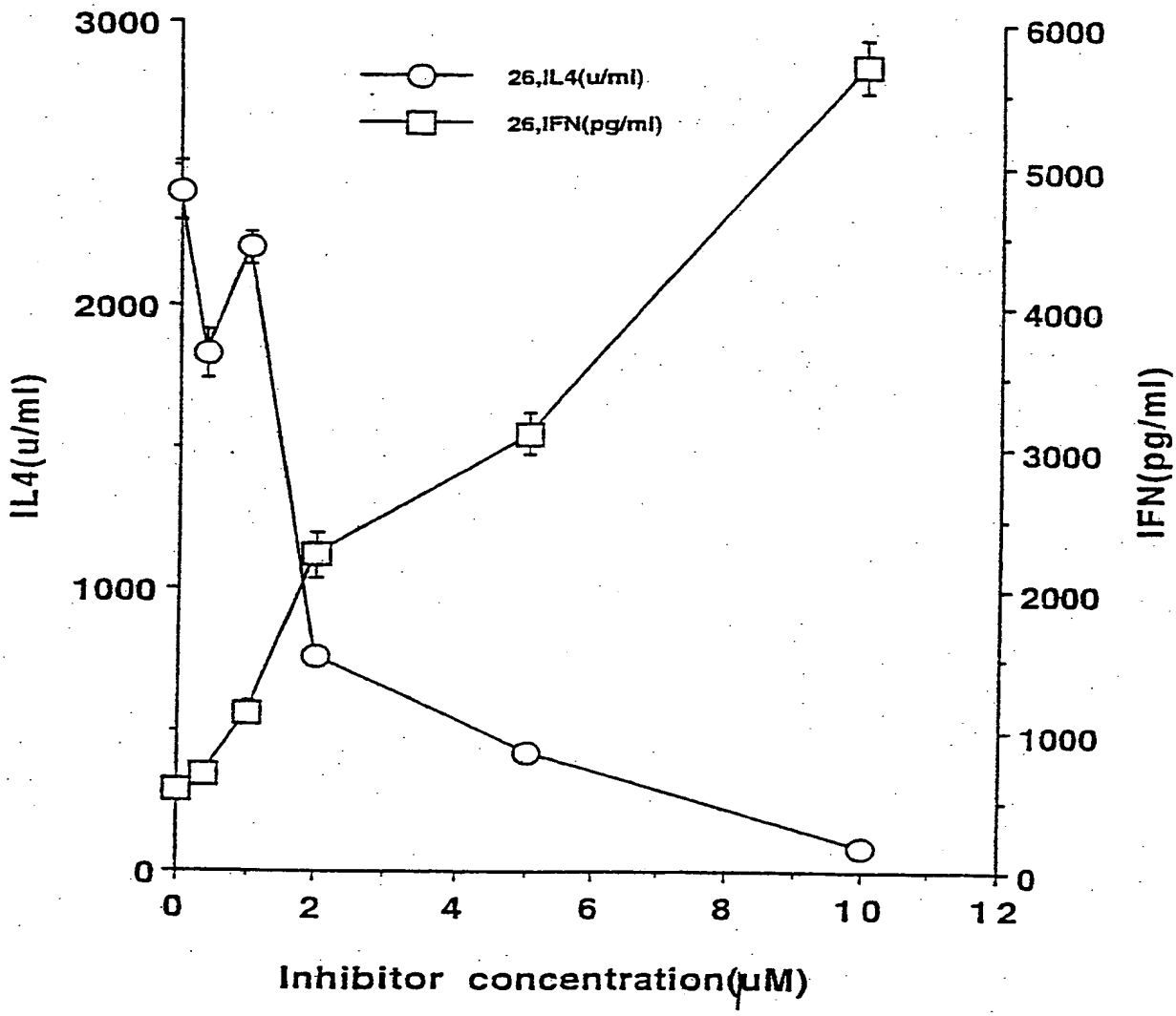

Figure 6

SEQUENCE LISTING

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<151> 1998-09-25

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1 5 10 15
Lys Val Leu

<210> 29
<211> 19
<212> PRT
<213> unknown

<220>
<223> CDC 5

<400> 29
Leu Glu Ile Cys Pro Asn Gly Ser Leu Met Glu Leu Leu Lys Arg Arg
1 5 10 15
Lys Val Leu

<210> 30
<211> 20
<212> PRT
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<220>
<223> Sak

<400> 30
Leu Glu Met Cys His Asn Gly Glu Met Asn Arg Tyr Leu Lys Asn Arg
1 5 10 15
Val Lys Pro Phe
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<210> 31
<211> 19
<212> PRT
<213> unknown

<220>
<223> Prk

<400> 31
Leu Glu Leu Cys Ser Arg Lys Ser Leu Ala His Ile Trp Lys Ala Arg
1 5 10 15
His Thr Leu

<210> 32
<211> 19
<212> PRT
<213> unknown

<220>
<223> Plo1

<400> 32
Leu Glu Leu Cys Glu His Lys Ser Leu Met Glu Leu Leu Arg Lys Arg
1 5 10 15
Lys Gln Leu

<210> 33
<211> 19
<212> PRT
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<220>
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<400> 33
Met Glu Tyr Ala Ser Gly Gly Glu Val Phe Asp Tyr Leu Val Ala His
1 5 10 15
Gly Arg Met

<210> 34
<211> 19
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<220>
<223> P78

<400> 34
Met Glu Tyr Ala Ser Gly Gly Glu Val Phe Asp Tyr Leu Val Ala His
1 5 10 15
Gly Arg Met

<210> 35
<211> 20
<212> PRT
<213> unknown

<220>
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<400> 35
Phe Glu Phe Leu His Gln Asp Leu Lys Lys Phe Met Asp Ala Ser Ala
1 5 10 15
Leu Thr Gly Ile
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<210> 36
<211> 20
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<220>
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<400> 36
Phe Glu His Val Asp Gln Asp Leu Arg Thr Tyr Leu Asp Lys Ala Pro
1 5 10 15
Pro Pro Gly Leu
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<210> 37
<211> 20
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<220>
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<400> 37
Phe Glu His Val Asp Gln Asp Leu Thr Thr Tyr Leu Asp Lys Val Pro
1 5 10 15
Glu Pro Gly Val
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<210> 38
<211> 21
<212> PRT
<213> unknown

<220>
<223> c-Src

<400> 38
Thr Glu Tyr Met Ser Lys Gly Ser Leu Leu Asp Phe Leu Lys Gly Glu
1 5 10 15
Thr Gly Lys Tyr Leu
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<210> 39
<211> 21
<212> PRT
<213> unknown

<220>
<223> c-Yes

<400> 39

Thr Glu Phe Met Ser Lys Gly Ser Leu Leu Asp Phe Leu Lys Glu Gly
1 5 10 15
Asp Gly Lys Tyr Leu
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<210> 40
<211> 21
<212> PRT
<213> unknown

<220>
<223> Fyn

<400> 40
Thr Glu Tyr Met Asn Lys Gly Ser Leu Leu Asp Phe Leu Lys Asp Gly
1 5 10 15
Glu Gly Arg Ala Leu
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<210> 41
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<212> PRT
<213> unknown

<220>
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<400> 41
Thr Glu Phe Met Cys His Gly Ser Leu Leu Asp Phe Leu Lys Asn Pro
1 5 10 15
Glu Gly Gln Asp Leu
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<210> 42
<211> 21
<212> PRT
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<220>
<223> Lyn

<400> 42
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1 5 10 15
Glu Gly Gly Lys Val
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<210> 43
<211> 21
<212> PRT
<213> unknown

<220>
<223> Hck

<400> 43
Thr Glu Phe Met Ala Lys Gly Ser Leu Leu Asp Phe Leu Lys Ser Asp
1 5 10 15
Glu Gly Ser Lys Gln
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<210> 44

<211> 21
<212> PRT
<213> unknown

<220>
<223> Lck

<400> 44
Thr Glu Tyr Met Glu Asn Gly Ser Leu Val Asp Phe Leu Lys Thr Pro
1 5 10 15
Ser Gly Ile Lys Leu
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<210> 45
<211> 21
<212> PRT
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<220>
<223> Csk

<400> 45
Thr Glu Tyr Met Ala Lys Gly Ser Leu Val Asp Tyr Leu Arg Ser Arg
1 5 10 15
Gly Arg Ser Val Leu
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<210> 46
<211> 21
<212> PRT
<213> unknown

<220>
<223> MatK

<400> 46
Met Glu His Val Ser Lys Gly Asn Leu Val Asn Phe Leu Arg Thr Arg
1 5 10 15
Gly Arg Ala Leu Val
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<210> 47
<211> 20
<212> PRT
<213> unknown

<220>
<223> Fak

<400> 47
Met Glu Leu Cys Thr Leu Gly Glu Leu Arg Ser Phe Leu Gln Val Arg
1 5 10 15
Lys Tyr Ser Leu
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<210> 48
<211> 21
<212> PRT
<213> unknown

<220>
<223> c-Abl

<400> 48
Thr Glu Phe Met Thr Tyr Gly Asn Leu Leu Asp Tyr Leu Arg Glu Cys
1 5 10 15
Asn Arg Gln Glu Val
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<210> 49
<211> 35
<212> PRT
<213> unknown

<220>
<223> Tie

<400> 49
Ile Glu Tyr Ala Pro Tyr Gly Asn Leu Leu Asp Phe Leu Arg Lys Ser
1 5 10 15
Arg Val Leu Glu Thr Asp Pro Ala Phe Ala Arg Glu His Gly Thr Ala
20 25 30
Ser Thr Leu
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<210> 50
<211> 35
<212> PRT
<213> unknown

<220>
<223> Tek

<400> 50
Ile Glu Tyr Ala Pro His Gly Asn Leu Leu Asp Phe Leu Arg Lys Ser
1 5 10 15
Arg Val Leu Glu Thr Asp Pro Ala Phe Ala Ile Ala Asn Ser Thr Ala
20 25 30
Ser Thr Leu
35

<210> 51
<211> 35
<212> PRT
<213> unknown

<220>
<223> Flg

<400> 51
Val Glu Tyr Ala Ser Lys Gly Asn Leu Arg Glu Tyr Leu Gln Ala Arg
1 5 10 15
Arg Pro Pro Gly Leu Glu Tyr Cys Tyr Asn Pro Ser His Asn Pro Glu
20 25 30
Glu Gln Leu
35

<210> 52
<211> 35
<212> PRT

<213> unknown

<220>
<223> Bek

<400> 52
Val Glu Tyr Ala Ser Lys Gly Asn Leu Arg Glu Tyr Leu Arg Ala Arg
1 5 10 15
Arg Pro Pro Gly Met Glu Tyr Ser Tyr Asp Ile Asn Arg Val Pro Glu
20 25 30
Glu Gln Met
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<210> 53
<211> 35
<212> PRT
<213> unknown

<220>
<223> FGFR-3

<400> 53
Val Glu Tyr Ala Ala Lys Gly Asn Leu Arg Glu Phe Leu Arg Ala Arg
1 5 10 15
Arg Pro Pro Gly Leu Asp Tyr Ser Phe Asp Thr Cys Lys Pro Pro Glu
20 25 30
Glu Gln Leu
35

<210> 54
<211> 35
<212> PRT
<213> unknown

<220>
<223> FGFR-4

<400> 54
Val Glu Cys Ala Ala Lys Gly Asn Leu Arg Glu Phe Leu Arg Ala Arg
1 5 10 15
Arg Pro Pro Gly Pro Asp Leu Ser Pro Asp Gly Pro Arg Ser Ser Glu
20 25 30
Gly Pro Leu
35

<210> 55
<211> 40
<212> PRT
<213> unknown

<220>
<223> PDGFR-a

<400> 55
Thr Glu Tyr Cys Phe Tyr Gly Asp Leu Val Asn Tyr Leu His Lys Asn
1 5 10 15
Arg Asp Ser Phe Leu Ser His His Pro Glu Lys Pro Lys Lys Glu Leu
20 25 30
Asp Ile Phe Gly Leu Asn Pro Ala
35 40

<210> 56
<211> 40
<212> PRT
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<220>
<223> PDGFR-b

<400> 56
Thr Glu Tyr Cys Arg Tyr Gly Asp Leu Val Asp Tyr Leu His Arg Asn
1 5 10 15
Lys His Thr Phe Leu Gln His His Ser Asp Lys Arg Arg Pro Pro Ser
20 25 30
Ala Glu Leu Tyr Ser Asn Ala Leu
35 40

<210> 57
<211> 40
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<213> unknown

<220>
<223> Flt-1

<400> 57
Val Glu Tyr Cys Lys Tyr Gly Asn Leu Ser Asn Tyr Leu Lys Ser Lys
1 5 10 15
Arg Asp Leu Phe Phe Leu Asn Lys Asp Ala Ala Leu His Met Glu Pro
20 25 30
Lys Lys Glu Lys Met Glu Pro Gly
35 40

<210> 58
<211> 40
<212> PRT
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<220>
<223> Flt4

<400> 58
Val Glu Phe Cys Lys Tyr Gly Asn Leu Ser Asn Phe Leu Arg Ala Lys
1 5 10 15
Arg Asp Ala Phe Ser Pro Cys Ala Glu Lys Ser Pro Glu Gln Arg Gly
20 25 30
Arg Phe Arg Ala Met Val Glu Leu
35 40

<210> 59
<211> 40
<212> PRT
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<220>
<223> Flk1

<400> 59
Val Glu Phe Ser Lys Phe Gly Asn Leu Ser Thr Tyr Leu Arg Gly Lys
1 5 10 15
Arg Asn Glu Phe Val Pro Tyr Lys Ser Lys Gly Ala Arg Phe Arg Gln

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Gly Lys Asp Tyr Val Gly Glu Leu
        35                  40

      <210> 60
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      <212> PRT
      <213> unknown

      <220>
      <223> c-Met

      <400> 60
Leu Pro Tyr Met Lys His Gly Asp Leu Arg Asn Phe Ile Arg Asn Glu
 1               5                  10                  15
Thr His Asn Pro
            20

      <210> 61
      <211> 20
      <212> PRT
      <213> unknown

      <220>
      <223> c-Sea

      <400> 61
Leu Pro Tyr Met Arg His Gly Asp Leu Arg His Phe Ile Arg Ala Gln
 1               5                  10                  15
Glu Arg Ser Pro
            20

      <210> 62
      <211> 20
      <212> PRT
      <213> unknown

      <220>
      <223> Ron

      <400> 62
Leu Pro Tyr Met Cys His Gly Asp Leu Leu Gln Phe Ile Arg Ser Pro
 1               5                  10                  15
Gln Arg Asn Pro
            20

      <210> 63
      <211> 20
      <212> PRT
      <213> unknown

      <220>
      <223> EGFR


      <400> 63
Thr Gln Leu Met Pro Phe Gly Cys Leu Leu Asp Tyr Val Arg Glu His
 1               5                  10                  15
Lys Asp Asn Ile
            20

      <210> 64
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<211> 20
<212> PRT
<213> unknown

<220>
<223> ErbB2

<400> 64
Thr Gln Leu Met Pro Tyr Gly Cys Leu Leu Asp His Val Arg Glu Asn
1 5 10 15
Arg Gly Arg Leu
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<210> 65
<211> 20
<212> PRT
<213> unknown

<220>
<223> ErbB3

<400> 65
Thr Gln Tyr Leu Pro Leu Gly Ser Leu Leu Asp His Val Arg Gln His
1 5 10 15
Arg Gly Ala Leu
20

<210> 66
<211> 20
<212> PRT
<213> unknown

<220>
<223> ErbB4

<400> 66
Thr Gln Leu Met Pro His Gly Cys Leu Leu Glu Tyr Val His Glu His
1 5 10 15
Lys Asp Asn Ile
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<210> 67
<211> 43
<212> PRT
<213> unknown

<220>
<223> Ret

<400> 67
Val Glu Tyr Ala Lys Tyr Gly Ser Leu Arg Gly Phe Leu Arg Glu Ser
1 5 10 15
Arg Lys Val Gly Pro Gly Tyr Leu Gly Ser Gly Gly Ser Arg Asn Ser
20 25 30
Ser Ser Leu Asp His Pro Asp Glu Arg Ala Leu
35 40

<210> 68
<211> 34
<212> PRT
<213> unknown

<220>
<223> TRK-NGFR

<400> 68
Phe Glu Tyr Met Arg His Gly Asp Leu Asn Arg Phe Leu Arg Ser His
1 5 10 15
Gly Pro Asp Ala Lys Leu Leu Ala Gly Gly Glu Asp Val Ala Pro Gly
20 25 30
Pro Leu

<210> 69
<211> 32
<212> PRT
<213> unknown

<220>
<223> TrkB

<400> 69
Phe Glu Tyr Met Lys His Gly Asp Leu Asn Lys Phe Leu Arg Ala His
1 5 10 15
Gly Pro Asp Ala Val Leu Met Ala Glu Gly Asn Pro Pro Thr Glu Leu
20 25 30

<210> 70
<211> 35
<212> PRT
<213> unknown

<220>
<223> TrkC

<400> 70
Phe Glu Tyr Met Lys His Gly Asp Leu Asn Lys Phe Leu Arg Ala His
1 5 10 15
Gly Pro Asp Ala Met Ile Leu Val Asp Gly Gln Pro Arg Gln Ala Lys
20 25 30
Gly Glu Leu
35

<210> 71
<211> 19
<212> PRT
<213> unknown

<220>
<223> Syk

<400> 71
Met Glu Met Ala Glu Leu Gly Pro Leu Asn Lys Tyr Leu Gln Gln Asn
1 5 10 15
Arg His Val

<210> 72
<211> 20
<212> PRT
<213> unknown

<220>
<223> Zap70

<400> 72
Met Glu Met Ala Gly Gly Gly Pro Leu His Lys Phe Leu Val Gly Lys
1 5 10 15
Arg Glu Glu Ile
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<210> 73
<211> 20
<212> PRT
<213> unknown

<220>
<223> Jak1

<400> 73
Met Glu Phe Leu Pro Ser Gly Ser Leu Lys Glu Tyr Leu Pro Lys Asn
1 5 10 15
Lys Asn Lys Ile
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<210> 74
<211> 20
<212> PRT
<213> unknown

<220>
<223> Jak2

<400> 74
Met Glu Tyr Leu Pro Tyr Gly Ser Leu Arg Asp Tyr Leu Gln Lys His
1 5 10 15
Lys Glu Arg Ile
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<210> 75
<211> 20
<212> PRT
<213> unknown

<220>
<223> Jak3

<400> 75
Met Glu Tyr Leu Pro Ser Gly Cys Leu Arg Asp Phe Leu Gln Arg His
1 5 10 15
Arg Ala Arg Leu
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<210> 76
<211> 18
<212> PRT
<213> unknown

<220>
<223> Tyk2

<400> 76
Met Glu Tyr Val Pro Leu Gly Ser Leu Arg Asp Tyr Leu Pro Arg His
1 5 10 15
Ser Ile

<210> 77
<211> 19
<212> PRT
<213> unknown

<220>
<223> Iak1

<400> 77
Leu Glu Tyr Ala Pro Leu Gly Thr Val Tyr Arg Glu Leu Gln Lys Leu
1 5 10 15
Ser Lys Phe

<210> 78
<211> 19
<212> PRT
<213> unknown

<220>
<223> Chk1

<400> 78
Leu Glu Tyr Cys Ser Gly Gly Glu Leu Phe Asp Arg Ile Glu Pro Asp
1 5 10 15
Ile Gly Met

<210> 79
<211> 22
<212> PRT
<213> unknown

<220>
<223> IKK-1

<400> 79
Met Glu Tyr Cys Ser Gly Gly Asp Leu Arg Lys Leu Leu Asn Lys Pro
1 5 10 15
Glu Asn Cys Cys Gly Leu
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<210> 80
<211> 22
<212> PRT
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<220>
<223> IKK-2

<400> 80
Met Glu Tyr Cys Gln Gly Gly Asp Leu Arg Lys Tyr Leu Asn Gln Phe

1 5 10 15
Glu Asn Cys Cys Gly Leu
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<210> 81
<211> 19
<212> PRT
<213> unknown

<220>
<223> DAPK

<400> 81
Leu Glu Leu Val Ala Gly Gly Glu Leu Phe Asp Phe Leu Ala Glu Lys
1 5 10 15
Glu Ser Leu

<210> 82
<211> 31
<212> PRT
<213> unknown

<220>
<223> IRK

<400> 82
Met Glu Leu Met Ala His Gly Asp Leu Lys Ser Tyr Leu Arg Ser Leu
1 5 10 15
Arg Pro Glu Ala Glu Asn Asn Pro Gly Arg Pro Pro Pro Thr Leu
20 25 30

<210> 83
<211> 18
<212> PRT
<213> unknown

<220>
<223> TGFbRII

<400> 83
Thr Ala Phe His Ala Lys Gly Asn Leu Gln Glu Tyr Leu Thr Arg His
1 5 10 15
Val Ile

<210> 84
<211> 18
<212> PRT
<213> unknown

<220>
<223> ACTRIIA

<400> 84
Thr Ala Phe His Glu Lys Gly Ser Leu Ser Asp Phe Leu Lys Ala Asn
1 5 10 15
Val Val

<210> 85
<211> 18
<212> PRT
<213> unknown

<220>
<223> ACTRIIB

<400> 85
Thr Ala Phe His Asp Lys Gly Ser Leu Thr Asp Tyr Leu Lys Gly Asn
1 5 10 15
Ile Ile

<210> 86
<211> 18
<212> PRT
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<220>
<223> ALK1

<400> 86
Thr His Tyr His Glu His Gly Ser Leu Tyr Asp Phe Leu Gln Arg Gln
1 5 10 15
Thr Leu

<210> 87
<211> 18
<212> PRT
<213> unknown

<220>
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<400> 87
Thr His Tyr His Glu Met Gly Ser Leu Tyr Asp Tyr Leu Gln Leu Thr
1 5 10 15
Thr Leu

<210> 88
<211> 18
<212> PRT
<213> unknown

<220>
<223> ALK3

<400> 88
Thr Asp Tyr His Glu Asn Gly Ser Leu Tyr Asp Phe Leu Lys Cys Ala
1 5 10 15
Thr Leu

<210> 89
<211> 18
<212> PRT

<213> unknown

<220>
<223> ALK4

<400> 89
Ser Asp Tyr His Glu His Gly Ser Leu Phe Asp Tyr Leu Asn Arg Tyr
1 5 10 15
Thr Val

<210> 90
<211> 18
<212> PRT
<213> unknown

<220>
<223> alk6

<400> 90
Thr Asp Tyr His Glu Asn Gly Ser Leu Tyr Asp Tyr Leu Lys Ser Thr
1 5 10 15
Thr Leu

<210> 91
<211> 18
<212> PRT
<213> unknown

<220>
<223> DDR1

<400> 91
Thr Asp Tyr Met Glu Asn Gly Asp Leu Asn Gln Phe Leu Ser Ala His
1 5 10 15
Gln Leu

<210> 92
<211> 18
<212> PRT
<213> unknown

<220>
<223> DDR2

<400> 92
Thr Glu Tyr Met Glu Asn Gly Asp Leu Asn Gln Phe Leu Ser Arg His
1 5 10 15
Glu Pro

<210> 93
<211> 21
<212> PRT
<213> unknown

<220>

<223> ILK

<400> 93
Thr His Trp Met Pro Tyr Gly Ser Leu Tyr Asn Val Leu His Glu Gly
1 5 10 15
Thr Asn Phe Val Val
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<210> 94
<211> 16
<212> PRT
<213> unknown

<220>
<223> JNK

<400> 94
Met Glu Leu Met Asp Ala Asn Leu Cys Gln Val Ile Gln Met Glu Leu
1 5 10 15

<210> 95
<211> 20
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<213> Artificial Sequence

<220>
<221> MYRISTATE
<222> (1)...(0)
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<221> AMIDATION
<222> (0)...(20)
<223> Akt1/Raca

<400> 95
Gly Met Glu Tyr Ala Asn Gly Gly Glu Leu Phe Phe His Leu Ser Arg
1 5 10 15
Glu Arg Val Phe
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<210> 96
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
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<222> (1)...(0)

<221> AMIDATION
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<223> Alk1

<400> 96
Gly Thr His Tyr His Glu His Gly Ser Leu Tyr Asp Phe Leu Gln Arg
1 5 10 15
Gln Thr Leu

<210> 97
<211> 22

<212> PRT
<213> Artificial Sequence

<220>
<221> ACETYLATION
<222> (1)...(0)

<221> AMIDATION
<222> (0)...(22)
<223> Braf

<400> 97
Lys Lys Lys Lys Lys Lys Gly Gly Ser Ser Leu Tyr His His Leu His
1 5 10 15
Ile Ile Glu Thr Lys Phe
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<210> 98
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<221> MYRISTATE
<222> (1)...(0)

<221> AMIDATION
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<223> Braf

<400> 98
Gly Thr Gln Trp Ser Glu Gly Ser Ser Leu Tyr His His Leu His Ile
1 5 10 15
Ile Glu Thr Lys Phe
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<210> 99
<211> 22
<212> PRT
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<220>
<221> MYRISTATE
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<221> AMIDATION
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<223> c-Abl

<400> 99
Gly Thr Glu Phe Met Thr Tyr Gly Asn Leu Leu Asp Tyr Leu Arg Glu
1 5 10 15
Cys Asn Arg Gln Glu Val
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<210> 100
<211> 21
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<220>
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<222> (1)...(0)

<221> AMIDATION
<222> (0)...(21)
<223> c-Met

<400> 100
Gly Leu Pro Tyr Met Lys His Gly Asp Leu Arg Asn Phe Ile Arg Asn
1 5 10 15
Glu Thr His Asn Pro
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<210> 101
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<221> MYRISTATE
<222> (1)...(0)

<221> AMIDATION
<222> (0)...(21)
<223> c-Raf

<400> 101
Gly Thr Gln Trp Ser Glu Gly Ser Ser Leu Tyr Lys His Leu His Val
1 5 10 15
Gln Glu Thr Lys Phe
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<210> 102
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<221> ACETYLATION
<222> (1)...(0)
<223> benzyl ester at position 11

<221> AMIDATION
<222> (0)...(14)
<223> c-Raf

<400> 102
Ser Ser Leu Tyr Lys His Leu His Val Gln Glu Thr Lys Phe
1 5 10

<210> 103
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<221> MYRISTATE
<222> (1)...(0)

<221> AMIDATION
<222> (0)...(21)
<223> c-Sea

<400> 103
Gly Leu Pro Tyr Met Arg His Gly Asp Leu Arg His Phe Ile Arg Ala
1 5 10 15
Gln Glu Arg Ser Pro
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<210> 104
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<221> MYRISTATE
<222> (1)...(0)

<221> AMIDATION
<222> (0)...(22)
<223> c-Src

<400> 104
Gly Thr Glu Tyr Met Ser Lys Gly Ser Leu Leu Asp Phe Leu Lys Gly
1 5 10 15
Glu Thr Gly Lys Tyr Leu
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<210> 105
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<221> ACETYLATION
<222> (1)...(0)
<223> benzyl ester at position 5
benzyl ester at position 9

<221> AMIDATION
<222> (0)...(14)
<223> c-Src

<400> 105
Gly Ser Leu Leu Asp Leu Lys Gly Glu Thr Gly Lys Phe Leu
1 5 10

<210> 106
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<221> MYRISTATE
<222> (1)...(0)

<221> AMIDATION
<222> (0)...(21)
<223> CDK2

<400> 106
Gly Phe Glu Phe Leu His Gln Asp Leu Lys Lys Phe Met Asp Ala Ser
1 5 10 15
Ala Leu Thr Gly Ile

20

<210> 107
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<221> ACETYLATION
<222> (1)...(0)
<223> benzyl ester at position 1
benzyl ester at position 7

<221> AMIDATION
<222> (0)...(14)
<223> CDK2

<400> 107
Asp Leu Lys Lys Phe Met Asp Ala Ser Ala Leu Thr Gly Met
1 5 10

<210> 108
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<221> ACETYLATION
<222> (1)...(0)
<223> benzyl ester at position 1
benzyl ester at position 7

<221> AMIDATION
<222> (0)...(14)
<223> CDK4

<400> 108
Asp Leu Arg Thr Tyr Leu Asp Lys Ala Pro Pro Pro Gly Leu
1 5 10

<210> 109
<211> 21
<212> PRT
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<220>
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<221> AMIDATION
<222> (0)...(21)
<223> CDK4

<400> 109
Gly Phe Glu His Val Asp Gln Asp Leu Arg Thr Tyr Leu Asp Lys Ala
1 5 10 15
Pro Pro Pro Gly Leu
20

<210> 110

<211> 21
<212> PRT
<213> Artificial Sequence

<220>
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<222> (1)...(0)

<221> AMIDATION
<222> (0)...(21)
<223> CDK6

<400> 110
Gly Phe Glu His Val Asp Gln Asp Leu Thr Thr Tyr Leu Asp Lys Val
1 5 10 15
Pro Glu Pro Gly Val
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<210> 111
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
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<222> (1)...(0)

<221> AMIDATION
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<223> Chk1

<400> 111
Gly Glu Tyr Ser Ser Gly Gly Glu Leu Phe Asp Arg Ile Glu Pro Asp
1 5 10 15
Ile Gly Met

<210> 112
<211> 19
<212> PRT
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<222> (1)...(0)

<221> AMIDATION
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<223> Chk1

<400> 112
Gly Glu Tyr Ala Ser Gly Gly Glu Leu Phe Asp Arg Ile Glu Pro Asp
1 5 10 15
Ile Gly Met

<210> 113
<211> 19
<212> PRT
<213> Artificial Sequence

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<222> (1)...(0)

<221> AMIDATION
<222> (0)...(19)
<223> CK IIa

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1 5 10 15
Gln Thr Leu

<210> 114
<211> 17
<212> PRT
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<220>
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<221> AMIDATION
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Gly Phe Glu His Val Asn Asn Thr Asp Phe Lys Gln Leu Tyr Gln Thr
1 5 10 15
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<210> 115
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<221> AMIDATION
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<223> Csk

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Gly Thr Glu Tyr Met Ala Lys Gly Ser Leu Val Asp Tyr Leu Arg Ser
1 5 10 15
Arg Gly Arg Ser Val Leu
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<210> 116
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<220>
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<223> benzyl ester at position 5

<221> AMIDATION
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<223> Csk

<400> 116
Gly Ser Leu Val Asp Leu Arg Ser Arg Gly Arg Ser Val Leu
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<210> 117
<211> 21
<212> PRT
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<220>
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<221> AMIDATION
<222> (0)...(21)
<223> Fak

<400> 117
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Arg Lys Tyr Ser Leu
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<210> 118
<211> 17
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<221> AMIDATION
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<223> FGFR-3

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1 5 10 15
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<210> 119
<211> 16
<212> PRT
<213> Artificial Sequence

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benzyl ester at position 16

<221> AMIDATION
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<223> FGFR-3

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<221> AMIDATION
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1 5 10 15
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<210> 121
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<221> AMIDATION
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1 5 10

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<211> 23
<212> PRT
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<221> AMIDATION
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<223> Flk1

<400> 122
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1 5 10 15
Lys Arg Asn Leu Phe Val Pro
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<210> 123
<211> 17
<212> PRT

<213> Artificial Sequence

<220>
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<221> AMIDATION
<222> (0)...(17)
<223> Flk1

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<210> 124
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<220>
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<221> AMIDATION
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<210> 125
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<213> Artificial Sequence

<220>
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<221> AMIDATION
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<400> 125
Gly Arg Phe Arg Gln Gly Lys Asp Tyr Val Gly Glu Leu
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<210> 126
<211> 22
<212> PRT
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<221> AMIDATION
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<223> GSK3b

<400> 126
Lys Lys Lys Lys Lys Lys Gly Gly Gly Val Ala Arg His Tyr Ser Arg
1 5 10 15
Ala Lys Gln Thr Leu Pro
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<210> 127
<211> 13
<212> PRT
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<221> AMIDATION
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<223> GSK3b

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1 5 10

<210> 128
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<220>
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<221> AMIDATION
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<223> GSK3b

<400> 128
Gly Asp Tyr Val Pro Glu Thr Val Tyr Arg Val Ala Arg His Tyr Ser
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Arg Ala Lys Gln Thr Leu
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<211> 12
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<400> 129
Arg Val Ala Arg His Tyr Ser Arg Ala Lys Gln Thr
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<211> 22
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Gly Thr Glu Phe Met Ala Lys Gly Ser Leu Leu Asp Phe Leu Lys Ser
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Asp Glu Gly Ser Lys Gln
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<210> 131
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<221> AMIDATION
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<223> Iak1

<400> 131
Gly Leu Glu Tyr Ala Pro Leu Gly Thr Val Tyr Arg Glu Leu Gln Lys
1 5 10 15
Leu Ser Lys Phe
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<210> 132
<211> 23
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<221> AMIDATION
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<400> 132
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1 5 10 15
Pro Glu Asn Ser Ser Gly Leu
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<210> 133
<211> 23
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<221> AMIDATION

<222> (0)...(23)
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<400> 133
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1 5 10 15
Phe Glu Asn Ser Ser Gly Leu
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<400> 134
Gly Thr His Trp Met Pro Tyr Gly Ser Leu Tyr Asn Val Leu His Glu
1 5 10 15
Gly Thr Asn Phe Val Val
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<221> AMIDATION
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<400> 135
Gly Tyr Asn Val Leu His Glu Gly Thr Asn Phe Val Val
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<210> 136
<211> 19
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<221> AMIDATION
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<223> IRK

<400> 136
Gly Met Glu Leu Met Ala His Gly Asp Leu Lys Ser Tyr Leu Arg Ser
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Leu Arg Pro

<210> 137
<211> 12
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<221> AMIDATION
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<400> 137
Ala Gln Asn Asn Pro Gly Arg Pro Pro Pro Thr Leu
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<400> 138
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<210> 139
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<210> 140
<211> 17
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<221> AMIDATION
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<400> 140
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Leu

<210> 141
<211> 21
<212> PRT
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<221> AMIDATION
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Asn Lys Asn Lys Ile
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<210> 142
<211> 13
<212> PRT
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<221> AMIDATION
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<223> Jak1

<400> 142
Gly Leu Lys Glu Tyr Leu Pro Lys Asn Lys Asn Lys Ile
1 5 10

<210> 143
<211> 13
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<221> AMIDATION
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<223> Jak2

<400> 143
Gly Leu Arg Asp Tyr Leu Gln Lys His Lys Glu Arg Ile
1 5 10

<210> 144
<211> 11
<212> PRT
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<220>
<223> stearyl at position 1

<221> AMIDATION
<222> (0)...(11)
<223> Jak2

<400> 144
Gly Leu Arg Asp Tyr Leu Gln Lys His Lys Glu
1 5 10

<210> 145
<211> 20
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<221> AMIDATION
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<223> Jak3

<400> 145
Gly Met Glu Tyr Leu Pro Ser Gly Ser Leu Arg Asp Phe Leu Gln Arg
1 5 10 15
His Arg Ala Leu
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<210> 146
<211> 21
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<221> AMIDATION
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<223> Jak3

<400> 146
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1 5 10 15
His Arg Ala Arg Leu
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<210> 147
<211> 13
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<221> AMIDATION
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<223> Jak3

<400> 147
Gly Leu Arg Asp Phe Leu Gln Arg His Arg Ala Arg Leu
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<210> 148
<211> 14
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<221> AMIDATION
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<223> Lck

<400> 148
Gly Ser Leu Val Asp Leu Lys Thr Pro Ser Gly Ile Lys Leu
1 5 10

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<221> AMIDATION
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1 5 10 15
Pro Ser Gly Ile Lys Leu
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<210> 150
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<223> Lyn

<400> 150
Gly Thr Glu Tyr Met Ala Lys Gly Ser Leu Leu Asp Phe Leu Lys Ser
1 5 10 15
Asp Glu Gly Gly Lys Val
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<210> 151
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<221> AMIDATION
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1 5 10 15
His Gly Arg Met
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<210> 152
<211> 15
<212> PRT
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<223> benzyl ester at position 2
benzyl ester at position 5

<221> AMIDATION
<222> (0)...(15)
<223> PDGFR-b

<400> 152
Gly Asp Leu Val Asp Tyr Leu His Arg Asn Lys His Thr Phe Leu
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<210> 153
<211> 22
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<221> AMIDATION
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<223> PDGFR-b

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Gly Thr Glu Tyr Ser Arg Tyr Gly Asp Leu Val Asp Tyr Leu His Arg
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Asn Lys His Thr Phe Leu
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<210> 154
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<212> PRT
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<221> AMIDATION
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Gly Met Glu Tyr Val Asn Gly Gly Asp Leu Met Tyr His Ile Gln Gln
1 5 10 15
Val Gly Arg Phe
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<210> 155
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<221> AMIDATION
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<400> 155
Lys Lys Lys Lys Lys Lys Gly Gly Asp Leu Met Tyr His Ile Gln Gln
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Val Gly Arg Phe
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<210> 156
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<223> benzyl ester at position 5

<221> AMIDATION
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<400> 156
Arg Ser Leu Leu Glu Leu His Lys Arg Arg Lys Ala
1 5 10

<210> 157
<211> 13
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<223> benzyl ester at position 6

<221> AMIDATION
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<400> 157
Gly Arg Ser Leu Leu Glu Leu His Lys Arg Arg Lys Ala
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<211> 20
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<221> AMIDATION
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<223> Plk

<400> 158
Gly Leu Glu Leu Ser Arg Arg Arg Ser Leu Leu Glu Leu His Lys Arg
1 5 10 15
Arg Lys Ala Leu
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<210> 159
<211> 22
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<221> AMIDATION
<222> (0)...(22)
<223> Ret

<400> 159
Gly Val Glu Tyr Ala Lys Tyr Gly Ser Leu Arg Gly Phe Leu Arg Glu
1 5 10 15
Ser Arg Lys Val Gly Pro
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<210> 160

<211> 15
<212> PRT
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<223> benzyl ester at position 9

<221> AMIDATION
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<223> Ret

<400> 160
Gly Ser Leu Arg Gly Phe Leu Arg Glu Ser Arg Lys Val Gly Pro
1 5 10 15

<210> 161
<211> 21
<212> PRT
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<221> AMIDATION
<222> (0)...(21)
<223> Ron

<400> 161
Gly Leu Pro Tyr Met Cys His Gly Asp Leu Leu Gln Phe Ile Arg Ser
1 5 10 15
Pro Gln Arg Asn Pro
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<210> 162
<211> 20
<212> PRT
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<221> AMIDATION
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<223> SNK

<400> 162
Gly Leu Glu Tyr Ser Ser Arg Arg Ser Met Ala His Ile Leu Lys Ala
1 5 10 15
Arg Lys Val Leu
20

<210> 163
<211> 20
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<221> AMIDATION
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<223> Syk

<400> 163
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1 5 10 15
Asn Arg His Val
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<210> 164
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<221> AMIDATION
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<223> TGFbRII

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Gly Thr Ala Phe His Ala Lys Gly Asn Leu Gln Glu Tyr Leu Thr Arg
1 5 10 15
His Val Ile

<210> 165
<211> 25
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<222> (1)...(0)

<221> AMIDATION
<222> (0)...(25)
<223> TrkB

<400> 165
Gly Phe Glu Tyr Met Lys His Gly Asp Leu Asn Lys Phe Leu Arg Ala
1 5 10 15
His Gly Pro Asp Ala Val Leu Met Ala
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<210> 166
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
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<222> (1)...(0)

<221> AMIDATION
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<223> TrkB

<400> 166
Gly Leu Arg Ala His Gly Pro Asp Ala Val Leu Met Ala
1 5 10

<210> 167
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> MYRISTATE
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<221> AMIDATION
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<223> TrkB

<400> 167
Gly Leu Arg Ala His Gly Pro Asp Ala Val Leu
1 5 10

<210> 168
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<223> TrkB

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Gly Leu Asn Phe Lys Leu Arg Ala His Gly Pro Asp Ala
1 5 10

<210> 169
<211> 13
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<222> (1)...(0)

<221> AMIDATION
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<223> TrkB

<400> 169
Gly Phe Lys Leu Arg Ala His Gly Pro Asp Ala Val Leu
1 5 10

<210> 170
<211> 21
<212> PRT
<213> Artificial Sequence

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<221> AMIDATION
<222> (0)...(21)
<223> Zap70

<400> 170
Gly Met Glu Met Ala Gly Gly Gly Pro Leu His Lys Phe Leu Val Gly
1 5 10 15
Lys Arg Glu Glu Ile
20

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/22106

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N9/12 G01N33/68 A61K38/45 A61P35/00 A61P37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N G01N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 25341 A (ST VINCENTS INST MED RES ;DARTMOUTH COLLEGE (US); KEMP BRUCE E (AU)) 17 July 1997 (1997-07-17) page 3, line 26 -page 4, line 3 seq id 28 page 4, line 22 -page 5, line 20 ---	1-24,63
X	WO 98 32017 A (TERRAPIN TECH INC) 23 July 1998 (1998-07-23) claims; examples; table 2 ---	1-24,44, 45,63
A	WO 94 07913 A (WARNER LAMBERT CO) 14 April 1994 (1994-04-14) -----	1-24

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 February 2000	15/02/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fuhr, C

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/ 22106

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 63 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 64-67
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 64-67

Present claims 1-63 relate to an extremely large number of possible compounds/products/methods. In fact, the claims contain so many options and possible permutations that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and/or concise), namely those compounds/products/methods recited in the examples and closely related homologous compounds. The search included peptides represented by the sequence ID's explicitely mentioned in the claims 26, 27, 29, 30, 32, 33, 35, 36, 38, 39, 41, 42, 44, 45, 47, 48, 50, 51, 53, 54, 56, 57, 59 and 60.

Present claims 64-65 relate to a method defined by reference to a desirable characteristic or property, namely a method for detecting ligands for protein kinases.
The claims cover all methods having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for none such methods. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the method by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the scope of claim impossible. Consequently, no search has been carried out for the claims relating to the method.

Present claims 66-67 relate to a compound and method defined by reference to a desirable characteristic or property, namely that its is an antibody to the alpha D region of a protein kinase and the method for producing it.
The claims cover all compounds and methods having this characteristic or property, whereas the application provides no support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds and methods. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the scope of claim is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound and method by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the scope of claim impossible. Consequently, no search has been carried out for the claims relating to antibodies and methods producing them.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte. ..tional Application No
PCT/US 99/22106

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